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.

PREMARKET TESTING GUIDELINES for FALLOPOSCOPES

DRAFT: November 20, 1992

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Introduction

This [draft] guideline is intended to serve as an aid in the preparation of a premarket approval application (PMA) for a falloposcope. In particular, the guideline outlines the information needed to fully and clearly describe the device, as well as to characterize all necessary preclinical and clinical testing of the device. The guideline also addresses professional and patient labeling needed to ensure that the falloposcope is used as safely and effectively as intended.

The falloposcope is a thin flexible endoscope that uses micro-fiberoptics for visualization with a conventional video monitor, as well as special catheter delivery technology to guide the endoscope through the cervix and uterus into the fallopian tube. The falloposcope is used to visualize the fallopian tube lumen of infertile women with obstructive tubal disease.

Direct visualization of the fallopian tube with a falloposcope may be clinically useful when used as an aid or adjunct to other diagnostic techniques for evaluating the fallopian tube, such as hysterosalpingography (HSG) or hydrochromotubation under laparoscopic observation. (See Section II, Clinical, for further discussion of the clinical utility of a falloposcope.)

This guideline is general in nature because of the anticipated diversity in falloposcope designs and the various anticipated ancillary devices used to introduce them into the fallopian tube. A manufacturer should use this guideline as an aid in developing testing protocols specific to its devices, as well as in the preparation of a PMA for such devices. For overall PMA guidance, manufacturers should also refer to FDA's Premarket Approval (PMA) Manual (HHS Publication FDA 87-4214) and Supplement (HHS Publication FDA 91-4245).

In order to develop the necessary clinical data, an investigational device exemptions (IDE) application may be required. For overall IDE guidance, refer to FDA's Investigational Device Exemptions: Regulatory Requirements for Medical Devices (HHS Publication FDA 89-4159).

MANUFACTURERS ARE STRONGLY ENCOURAGED TO CONSULT WITH FDA's OFFICE OF DEVICE EVALUATION REGARDING THE APPLICABILITY OF THIS [DRAFT] GUIDELINE TO THEIR OWN SPECIFIC FALLOPOSCOPE AND ANCILLARY DEVICES.

FDA is also aware that other intrafallopian technologies for diagnosis and/or treatment of tubal disease are currently under development. These include fluoroscopic tubal catheterization, hysteroscopically-directed tubal cannulation, transcervical balloon tuboplasty, and laparoscopically-directed salpingoscopic techniques. Further consultation with FDA is necessary for these advanced technologies.

Section I Preclinical

This section is intended to specify the appropriate descriptive/design, toxicological, chemical, mechanical, electrical, and optical information needed on the falloposcope and accessories, with emphasis on the necessary preclinical laboratory testing. (Some of this information is expected in an application for investigational device exemptions (IDE) to conduct clinical trials of the falloposcope.)

All preclinical testing of the device or components shall be performed on the finished sterilized device. For components intended to be reused, preclinical testing should be performed after repeated cleaning and sterilization or disinfection processing.

Specify any voluntary standards used to characterize the device or any components. If no standards exist to adequately address certain performance features of the device, provide rationale - in terms of clinical requirements - for the choice of performance specifications for these features.

A. Description of the Falloposcope and Accessories

1. Provide a complete description of the falloposcope, including each functional component. Refer to any applicable voluntary standards, e.g., ISO/DIS 8600. Provide a full description of the principle of operation of each component and the system as a whole. Provide detailed drawings and description of the falloposcope. If possible, include a sample of the device and its delivery catheter and/or videotapes illustrating its operation.

2. Provide rationale for design and dimension specifications, in light of known anatomical constraints of the human fallopian tube, based on relevant literature or sound theoretical reasoning.

3. Fully describe all accessory instruments, such as catheters and stylets, etc., used to introduce the falloposcope into the tube, as well as any devices used with the falloposcope, including imaging instrumentation, light source, etc.

B. Materials and Chemistry

1. Provide detailed information for all component materials used in the manufacture of the falloposcope and accessories. For each material, clearly identify the chemical composition, chemical and physical specifications, and material supplier(s). Identify all chemicals used to manufacture the device and fabricate device components, including solvents, lubricants, stabilizers, antioxidants, adhesives, etc.

2. Provide information to demonstrate that the manufacturing processes will not alter critical chemical and physical properties of the device materials. Where appropriate, include results of chemical evaluation of key materials used in the manufacture of the device, e.g., molecular weight and molecular weight distribution determinations, infrared (IR) analysis, and United States Pharmacopeia (USP) physico-chemical tests on material extract including, non-volatile residue and residue on ignition and heavy metals, etc.

C. Physical Properties

1. Provide a detailed description all components of the falloposcope delivery system, including any catheter, cannula, controls, and accessories, as well as the falloposcope itself. Identify all critical components. Describe the mechanics of operation for each individual component and the system as a whole.

2. Provide the results of engineering tests performed on a representative replicate number of components and/or systems consistent with the intended usage of the device. Provide rationale for test performance requirements relative to anticipated clinical conditions. This rationale should also address all important factors that may affect device performance, including sterilization or other preconditioning, anatomical configuration, applied loads, repeated deployment or usage, environment, time in environment or under load, etc.

    a. Mechanical strength - Evaluate all components, manufactured joints and connections for the following parameters:

        · static strength in tension
        · internal pressure, torsion, and/or bending, as appropriate.

        Failure modes should be identified as clean breaks or fragmentation. Safety factors relative to anticipated *in vivo* load should be reported.

    b. Determine the tear strength of any toposcopic membrane.

    c. Provide results from appropriate durability testing of the device consistent with its intended use. Specify and test the minimum recommended bend radius of the falloposcope (radius of curvature.

    d. Provide results from appropriate testing of force, torque, displacement or other relevant physical measurements, following simulated deployment and removal of the device through an anatomical model. Address both deliberate and inadvertent deployment and removal.

3. Provide test results on the mechanical integrity of the falloposcope, following repeated deployment through a simulated anatomical model.

D. Electrical Properties

1. Provide a complete description of the electronic design of all applicable components, such as electrical connections, power supplies for illumination systems and video displays. Include circuit and block diagrams. Address the safety of these components, including an identification of the means of electrical isolation of the component and connectors from the patient. Identify any relevant safety standards to which the device complies, e.g., IEC 601-1, UL 544, etc.

2. Identify all video components provided with the device or considered to be compatible with the device. This should include the video monitor, recording devices and connecting cables as applicable. If these components are not provided as part of the system, provide a full set of specifications for each component needed to make the

system fully operational. Include justification for these specifications.

If any of the above instrumentation uses computer-controlled components, e.g., imbedded software, microprocessors, etc., refer to FDA's guideline on these devices [REVIEWER GUIDANCE FOR COMPUTER CONTROLLED DEVICES UNDERGOING 510(k) REVIEW (August 29, 1991)].

E. Illumination

Describe the following:

1. type of light source(s) used for target illumination, e.g., tungsten halogen, xenon arc, etc. Provide information on the primary purpose of the illumination, e.g., human visualization, video, flash photography, etc.;

2. range of illumination levels at the target (ft-cd);

3. spectral irradiance of the illumination delivered to the target (W/cm^2; if changing the illumination level changes the spectrum of illumination, provide the additional spectral irradiance data; if multiple sources are used, provide the combined spectral irradiance at the target; and

4. divergence of illumination beam (degrees).

F. Optical Properties

1. Provide all specifications on the optical performance of the falloposcope micro-optical system, under both optimum conditions (straight fiber, clear field) and realistic conditions (tortuous path, natural fluids), to include the following:

   - magnification of the imaging system(s)
   - focal length (mm)
   - optical resolution, viewing a 3 bar resolution target USAF 1951 (lp/mm)
   - depth of field (mm)
   - field of view (degrees)
   - direction of view (degrees)
   - spectral transmission of the optical system
   - typical image luminance level (ft-cd)
   - minimum recommended bend radius (mm)

2. Provide rationale and describe all testing performed to establish these specifications. Identify any relevant standards to which the device complies, e.g., USAF 1951 resolution chart, etc.

3. Provide statistically valid results of operator performance testing to fully assess the optical/visualization capabilities of the falloposcope. An appropriate number of normal-visioned operators should use the falloposcope to identify appropriate resolution charts under both optimum conditions (straight fiber, clear field) and realistic conditions (tortuous path, natural fluids). Repeat testing of optical performance should be performed after physically cycling the device through the anatomical model a number of times, with cleaning and sterilization performed between each cycle. Cycle number should be at least as great as the mean number of anticipated cycles during the anticipated life of the device. See Section I,

Part H(2)(b) below.

G. Toxicology

Provide the protocols, as well as test data and conclusions, from the toxicological testing of the falloposcope and introduction instruments. Refer to FDA's Tripartite Biocompatibility for Medical Devices Guidance for selecting the appropriate types of tests. For specific guidance on the appropriate testing for each device, you may contact Raju G. Kammula, D.V.M., Ph.D. at (301) 427-1287.

H. Cleaning, Sterilization, Disinfection, and Reuse

1. Sterile, Single-Use/Disposable

For each system component provided as a sterile, single-use/disposable, provide a complete description of the sterilization procedure and cycle. Provide a complete description of the analytical methods for qualifying, and validating the sterilization cycle. Provide the supporting data, including calculations demonstrating the sterility assurance level (SAL). It may be useful to refer to the Association for the Advancement of Medical Instrumentation (AAMI) sterilization guidelines.

2. Reusable Parts

a. For each system component intended for reuse, provide a complete description of the recommended procedures for cleaning and sterilization or disinfection. Provide a complete description of the analytical methods for qualifying and validating these recommended procedures. Provide the supporting data, including calculations demonstrating the sterility assurance level (SAL). It may be useful to refer to the AAMI sterilization guidelines. Perform validation testing on devices that have undergone repeated exposure to the intended biological environment or an appropriate model representative of the biological environment.

b. Confirm acceptable device performance characteristics after repeated exposure to the biological environment, cleaning and sterilization or disinfection. Identify "markers" for the clinician to use to determine the serviceable life of the device.

I. Shelf-Life for Sterile, Single-Use/Disposable

For each system accessory intended as a sterile, single-use/disposable, provide results from appropriate performance and sterility testing to demonstrate the recommended shelf-life of that component. Provide rationale for test methodology.

Section II Clinical

An analysis of the clinical utility of the device must be considered by the device manufacturer. The analysis should take into consideration the clinical benefit of direct fallopian tube visualization including an explanation of how visualization will aid the clinician in a diagnosis and how this will lead to more effective treatment.

In developing the clinical protocol for investigation of the device, appropriate controls for the device under investigation should be considered. We suggest a comparison of the results of treatment with a control (including historical control) or standard to permit quantitative evaluation. Generally, four types of comparison groups are recognized:

1) No treatments
2) Placebo control
3) Active treatment control
4) Historical control

Historical controls are the weakest type of controls from a statistical viewpoint because it is very difficult to assure comparability of important prognostic variables with the treated group, especially if the disease or therapy has changed over time.

Randomization must be considered and, if not practical, significant justification must be provided. Objective scoring systems for the diagnosis of tubal disease must be developed for direct visualization of the fallopian tube which allows comparison to contemporary indirect diagnostic means, e.g., hysterosalpingography and hydrochromotubation.

A. Feasibility Study (Phase I)

Objective

Appropriate Phase I studies of the device must be conducted to determine the feasibility of the falloposcope by evaluating in a small population the safety and effectiveness of the device with respect to the following concerns:

Safety

- trauma
- infection
- bleeding
- uterine and/or tubal perforation
- pain and discomfort

Effectiveness

- Difficulty/Ease of Introduction
- Adequate Visualization

The Phase I clinical trial should evaluate device performance for tubal visualization, as well as tissue effects of intrafallopian introduction of such instrumentation. Appropriate post-operative histopathology studies should be conducted to evaluate the effects of the falloposcope and introducing catheter on the tubal lumen, cilia, etc.

The Phase I trial should also incorporate operator performance testing, as specified in I(F)(3) of the Preclinical Section above, to evaluate

large and small tubal blockage, as well as disease site and state.

Patient Selection and Exclusion Criteria

Study subjects for the feasibility study should have some evidence of tubal blockage and be hysterectomy candidates. Age? Parity?

Subjects should be excluded from the study for the following reasons:

- pregnancy
- acute infection
- systemic conditions contraindicating surgery, such as cardiovascular disease, severe pulmonary disease, etc.

Investigator Selection Criteria

Investigators should be experienced hysteroscopists, knowledgeable in the management of infertility patients and experienced in the diagnosis and treatment of fallopian tube disease.

Study Size, Duration, and Follow-up

Phase I should include at least 20, and no more than 50, study subjects.

Study Duration?
Type and Length of Follow-up?

B. Safety and Effectiveness Study (Phase II)

Objective: **Must be Defined - With respect for the requirement to demonstrate clinical benefit**

In developing the clinical protocol for investigation of the falloposcope, appropriate controls should be considered. Any PMA should contain results of patient management with a control (including historical control) or standard in order to permit quantitative evaluation. Generally, four types of comparison groups are recognized:

(1) No treatments

(2) Placebo control

(3) Active treatment control

(4) Historical control

Historical controls are the weakest type of controls from a statistical viewpoint because it is very difficult to ensure comparability of important prognostic variables with the treated group, especially if the disease or management regimen has changed over time.

PANEL COMMENT:

- Endpoint with Clinical Significance?
- Randomized Controlled Clinical Trials?
- Study Subject Selection Criteria?
- Study Subject Exclusion Criteria?

- Investigator Selection Criteria?
- Study Size, Duration, Length and Type of Follow-up?
- Statistical Evaluation?
- Data Collection?

Section III Manufacturing

Provide detailed description of the methods used to manufacture each component of the device. [Provide reference to guidelines.]

Section IV Post Market Surveillance & Post Approval Studies

During data collection and review of the premarket approval (PMA) application, FDA may identify unforeseen device-related adverse effects. FDA, in consultation with its advisory Panel, may impose postapproval requirements to obtain further information, including postmarket surveillance and/or post-approval studies.

Section V Labeling

Labeling must contain a complete description of the device and all relevant appropriate findings from preclinical and clinical studies. Based on these findings, labeling must clearly delineate the indication(s) for use, contraindications, warnings, and precautions, as well as clinical instructions for use. The labeling must identify appropriate methods for cleaning, disinfection and sterilization of the fiberoptic system, as well as methods for evaluating performance and criteria for determining inadequate performance. Both professional and patient labeling must be prepared.

Manufacturers are encouraged to consult with FDA's manual "Labeling: Regulatory Requirements for Medical Devices", (HHS Publication FDA 89-4203).