Guidance for Industry

Electro-optical Sensors for the *In Vivo* Detection of Cervical Cancer and its Precursors:

Submission Guidance for an IDE/PMA

Draft Guidance – Not for Implementation

This guidance document is being distributed for comment purposes only.
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U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Obstetrics and Gynecology Devices Branch
Division of Reproductive, Abdominal, Ear, Nose and Throat, and Radiological Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Mridulika Virmani, Ph.D., HFZ-470, 9200 Corporate Boulevard, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Mr. Colin M. Pollard at (301) 594-1180 or by electronic mail at CMP@CDRH.FDA.GOV.

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INTRODUCTION

Over the past few years, several manufacturers and sponsor/investigators have approached FDA with various types of hand-held probes that employ electro-optical sensor technology to optically interrogate the cervix uteri for cancer and its precursors. Many of these systems use complex signal discrimination algorithms and/or neural networks to differentiate abnormal from normal tissue. The current clinical approach for the early detection of cervical cancer starts with the routine screening of asymptomatic women via the PAP smear, with a series of follow-up steps (e.g., colposcopy, biopsy, etc.) in the event of an abnormal PAP finding. The new technology covered by this guidance document, depending upon design and study results, may ultimately complement (as an adjunct) or replace the PAP smear, or it may serve to improve the results of the colposcopy or biopsy. FDA has determined that this new technology poses new types of safety and effectiveness questions, compared to current technologies used to detect cervical cancer, and that a premarket approval (PMA) application is recommended.

This guidance document is also the result of several preliminary interactions between FDA and developers of these types of devices, as well as input from experts at a meeting of FDA's advisory committee, the Ob-Gyn Devices Panel, on July 14-15, 1997. As stated above, this guidance covers electro-optical devices applied to a woman's cervix in an *in vivo* setting that give a relatively instantaneous reading of the test results for the purposes of detection of cervical cancer and its precursors (hereinafter referred to as *in vivo* detection devices). This contrasts with the *in vitro* diagnostic (IVD) devices, such as automated cervical cytology readers used for primary screening, quality control and cervical cytology specimen preparation devices which are clinical laboratory type devices reviewed by FDA's Division of Clinical Laboratory Devices.

This document attempts to identify the basic elements that FDA expects to see addressed during development of the detection system and that would be included in a PMA application for such a device. Need for an IDE application to FDA is governed by the provisions in the IDE regulation on *Significant Risk* device investigations, 21 CFR 812.3(m). Please confer with the FDA contact given above regarding whether a particular device falls under this definition.

Please note that these *in vivo* detection devices apply several different optical phenomena, including auto-fluorescence and Raman spectroscopy. Some even include bioelectrical phenomena. It is important to understand that devices based on certain technologies may not require all of the information contained herein, whereas devices based on other technologies may require additional studies beyond the scope of this guidance document.

For general information about how to submit an IDE application, contact FDA's Center for Devices and Radiological Health's (CDRH) Division of Small Manufacturers Assistance (DSMA) at (800) 638-2041 or (301) 443-6597. You may also wish to view CDRH's new *Guidance For Industry: New Model Medical Device Development Process* on the World Wide Web – http://www.fda.gov/cdrh/pmat/newmod.html. The *Guidance* presents several different models for the development and review of Class III medical devices, including the informal pre-IDE review and the PMA shell/module approach.

The FDA welcomes comments on this draft guidance document and will consider all scientifically valid alternatives to the preclinical and clinical requirements stated within. ***Also, it is also highly recommended that the sponsor of a new investigation consult with the Obstetrics and Gynecology Devices Branch (OGDB) within the Office of Device Evaluation (ODE) prior to submission of an original IDE or PMA application, at (301) 594-1180.***

This guidance document represents the agency's current thinking on the appropriate content of IDE applications for *in vivo* devices for the detection of cervical cancer and/or its precursors. It does not create or confer any 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 statutes or regulations.

1 INTENDED USE

The type of clinical study necessary to support a premarket submission for an *in vivo* detection device will depend on the proposed indication for use. In general, sensors intending to replace the standard cervical/vaginal cytology Papanicolaou (Pap) smear as a primary screening tool will require a more stringent documentation of safety and effectiveness and a different type of clinical study than a sensor used as an adjunct or a secondary triage modality.

Indications for Use

The clinical study section of this guidance discusses the issues surrounding clinical study design for the indications that FDA has considered to date. It does not include all possible indications for these devices. If a manufacturer wishes to design a clinical study for a different indication, FDA will provide interactive feedback on the proposed clinical study design. This guidance document discusses the following four indications for use:

1 **Adjunct to the Cervical/Vaginal Cytology** - The sensor is used *in addition* to cervical/vaginal cytology for primary screening for cervical cancer and its precursors.

2 ASCUS Triage or Triage following an Abnormal Cervical / Vaginal Cytology Result – The sensor is used to determine which patients with abnormal cervical/vaginal cytology screening test results are referred to colposcopy or loop electro-surgical excision procedure (LEEP).

3 **Localize Biopsy Sites** – The sensor is used at the time of colposcopy to assist in the localization of biopsy sites.

4 **Primary Screening Device as an Alternative to Cervical / Vaginal Cytology**– The sensor is used as a replacement for cervical/vaginal cytology as a primary screening tool.

Principle of Operation

The sponsor of the IDE/PMA application should describe the principle of operation of the device. This description should address the questions posed below:

1 Does the device contact the cervix or is it a non-contact device?
2 Does the device read the entire cervix at once, or does the operator need to manually "scan" the cervix?
3 How does the operator ensure complete examination of the cervix?
   a) What are the dimensions of the area that the device "visualizes"?
   b) To what extent can the device 'view' the endocervix?
   c) Can the device distinguish the transformation zone?
   d) The labeling should clearly describe the limitations of what cannot be "visualized" by device.

2 DEVICE HAZARDS IDENTIFICATION/RISK ANALYSIS (SAFETY RISK MANAGEMENT)

The IDE/PMA sponsor should provide a complete description of all potential hazards, their consequences, and the probability of the hazard to the patient. Risk is determined by the probability of a hazard and the severity of its consequences. Additionally, the sponsor should identify any consensus standards or guidance used for this purpose.

An IDE application must be submitted to FDA for approval of a clinical investigation of a significant risk device. IDE regulations require a determination significant risk (SR) or nonsignificant risk (NSR), 21 CFR Part

812.3(m). The IDE regulations provide a definition of a significant risk device as one that presents a potential for serious risk to the health, safety or welfare of a study subject. A NSR device investigation is one that does not meet the definition for a significant risk study. Both SR and NSR devices require an investigational plan, adequate informed consent of the study subject, and approval from the local institutional review board (IRB). Additional guidance for making the SR/NSR determination is given later in this section. Please confer with Obstetrics and Gynecological Devices Branch (OGDB) staff if you have any questions.

For devices using lasers or other light sources, the possible adverse events due to photosensitivity, that may be known or unknown to the patient, e.g., drug photosensitivity, should also be addressed in this section. This section should identify all the foreseeable hazards including following:

- Optical radiation hazards (*This hazard/risk is discussed below, as this risk is specific to this type of device*)
- Thermal (heating) hazard
- Electrical shock hazard
- Electromagnetic compatibility (EMC)
- Software hazard
- Material toxicity hazard
- Clinical hazards of tissue trauma, bleeding, patient-to-patient transmission of STDs or other infections
- System-level hazard analysis

Electrical, EMC, software, and system level hazards analyses are discussed later in this document, in Section 3 on Device Specifications. The material toxicity hazards will be discussed in Section 4 on Preclinical Testing. Design considerations, as well as disinfection and sterilization methods, should mitigate patient-to-patient transfer of sexually transmitted diseases (STDs); this is discussed further in Section 4. Likewise, other clinical hazards, such as tissue trauma or bleeding, are addressed in Section 6 on Clinical Testing.

These types of electro-optical sensors may use a variety of light sources, including lasers, to emit light in the ultraviolet, infrared, near-infrared, and visible light spectra. These optical outputs can pose several risks, such as cancer, burns and other thermal effects, photosensitization (if woman has a photo-sensitizing disease or is taking a photo-sensitizing drug), and possible activation of latent infectious agents, etc. As discussed above, an early regulatory step for study sponsors will be to make a significant risk nonsignificant risk determination (21 CFR 812.3). Optical and thermal hazards are discussed below in greater detail in order to facilitate this determination.

Optical Radiation Hazards

For non-laser devices:

The sponsor should provide an analysis of the radiation emissions from its device, demonstrating that the biologically-effective radiation (i.e., the integral of the device emission spectrum weighted with the action spectrum published by the American Conference of Governmental Industrial Hygienists (ACGIH)) is below the ACGIH threshold limit value (TLV) of 0.003 J / cm^2 for ultraviolet radiation (250-400 nm). Broadband light sources emitting visible or infrared radiation (400 nm - $1x10^3$ μm) can be compared to the 'TLVs for the Skin Exposure from a Laser Beam' published by the ACGIH.

For laser devices or LEDs (Light Emitting Diodes):

The sponsor should provide measurement data demonstrating that the maximum *possible* patient exposure levels are <u>below</u> the maximum *permissible* exposure limits published by the American National Standards Institute (ANSI) **or** the 'TLVs for Skin Exposure from a Laser Beam' published by the ACGIH.

Special Circumstances Regarding Optical Radiation

The sponsor should consider any possible contraindications for use to minimize the likelihood of optical radiation hazards, such as:

- Patients with a photosensitizing disease, e.g., porphyria, lupus erythematosus
- Patients undergoing phototherapy
- Patients taking photosensitizing drugs

Thermal Safety

If the device has the potential for increasing the temperature of the cervix during diagnosis, the sponsor should provide evidence that there is no significant tissue heating or damage from any possible combined effects from optical radiation and other energy delivered to the tissue during the diagnostic procedure. This could be accomplished by examining endpoints like peak tissue temperature or tissue denaturation.

Manufacturers should provide data for thermal effects on the patient or user, which may result from use of optical radiation or electrical energies used alone, or simultaneously. In this section, effects of thermal changes should be considered such as inflammation, presence of blood, mucus, and for possible thermal activation or stimulation of human papilloma virus (HPV) or other viruses.

3 DEVICE SPECIFICATIONS

Device Description

The sponsor should provide a description of the overall design and detection logic of the device. The sponsor should also provide a complete description of the detection algorithm development.

Sponsors should provide device design, model and specifications including:

1. Fully dimensioned engineering drawings
2. Block diagram, including all inputs, output, and major processing steps
3. Complete characterization of all critical components
4. Description of user interface, including any parameters that the user can set
5. Discussion of safety features for patient and operator
6. Sample devices where feasible, photo, or a videotape showing the device in operation
7. Reproducibility of output that will support diagnostic results characterized on a stable test material and later on patients.
   (see section on optical calibration)

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 (21 CFR Part 73).

Software

In July of 1998, FDA issued a guidance document addressing overall concerns for devices containing software. This guidance spells out the type of documentation required for all kinds of devices, the level and detail of documentation following from the initial designation.

Using the general FDA guidance document, provide documentation describing the software development life cycle and risk management activities. This should include at a minimum:

1. Software requirements specification
2. System level test plan with pass-fail criteria and traceability to requirements

3. Results of system level testing
4. Summary of software Quality Assurance (QA) activities
5. Software hazard analysis

If the device will use Off-the-Shelf (OTS) software (e.g., Windows 95, DOS, digital signal processing software provided by a third party, etc.), the following additional information should be provided **for each OTS software component used:**

1. Title, manufacturer, version number and date
2. Hardware requirements for the OTS software
3. Function of the OTS software
4. Steps taken to validate intended use of OTS software
5. Discussion of why use of OTS software is appropriate given both the function of the OTS software, and the intended use and indications for use of the device.

FDA is currently developing a separate guidance document addressing issues associated with OTS software. You may check with our Division of Small Manufacturers Assistance (DSMA) regarding its availability, at 1-800-638-2041.

Labeling:

Provide samples of all device labeling. The labeling should include the following information (21 CFR Part 812.5):

1. Name and address of the manufacturer, packer, or distributor
2. Quantity of contents (if appropriate)
3. Directions for use
4. Reprocessing instructions
5. Description of all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions
6. For IDE submissions sponsor should provide The statement: "CAUTION - Investigational Device, limited by Federal law to investigational use."

Note: 21 CFR Part 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.

4. PRECLINICAL TESTING

Biocompatibility Testing (for patient-contacting devices)

The following biocompatibility testing should be performed on the final, finished device for all patient-contacting components. As per CDRH's 'Blue Book' memorandum #95-1; Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part I: 'Evaluation and Testing", these devices are surface devices, with a limited duration contact time to mucosal tissues. Tests should be conducted in conformance with Good Laboratory Practices (GLP) in accordance with 21 CFR Part 58.

1. Acute systemic toxicity
2. Cytotoxicity
3. Sensitization (with both polar and non-polar extracts)
4. Irritation (mucosal)

If the device is made of materials that have been well characterized chemically and physically in the published literature, and have a long history of safe use, FDA will accept adequate justification for not conducting some or all of the suggested tests.

For additional information on biocompatibility, please refer to the 'Blue Book' Memorandum #G95-1 Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing," available from Division of Small Manufacturers Assistance.

Characterization of Optical Radiation

I. Exposure time and exposure area - For all types of light sources (laser or non-laser), provide:

   1 Total possible exposure time or maximum number of pulses per examination site, and
   2 Size of irradiation zone on the cervix

II. Optical radiation emission from device

A. For devices using laser or light-emitting diodes (LEDs) provide the following information:

1. Peak emission wavelength (s) and bandwidth (Full Width at Half Maximum (FWHM) for emitters with bandwidth "greater than" 1.0 nm)
2. Peak power and average power as measured with NIST-traceable radiometer
3. Identify whether the source is pulsed or continuous - if pulsed, provide pulse width and pulse repetition rate

B. For devices using broadband sources, provide either:

1. Both relative spectral radiant output and absolute total radiant power output (W/cm^2) measured with a NIST-traceable calibrated instrument over the wavelength range 250-1100 nm

or

2. Absolute spectral irradiance ($W/(cm^2\text{-nm})$) over the wavelength range 250-1100 nm, as measured with a NIST traceable calibrated spectroradiometer.

In all cases, describe the measurement apparatus and calibration procedures, giving an estimate of the uncertainties associated with the measurement.

Optical Calibration

Calibration procedures should be instituted both at the production stage and in the clinic before each use. For the clinical test, complete instructions should be supplied to the user, and the device should clearly indicate the results of the calibration / self-test to the user.

Calibration should ensure that the device is operating properly, i.e. that there has been no degradation in performance since the device was first received from the manufacturer.

An optical phantom, or some other means, should be employed that sufficiently simulates the spectral / optical characteristics of the target tissue.

The sponsor should provide documentation that the proposed procedure for calibration clearly ensures that the device is capable of performing its intended function.

Electrical Safety

Provide either:

- Provide certification that the device complies with applicable electrical safety standards (e.g., IEC 60601-1, UL 2601); and Identify the standard.

or

Safety levels, test procedures, and test results which guarantee a similar level of protection.

Electromagnetic Compatibility (EMC)

Provide:

Certification that the device complies with applicable EMC standards (e.g., IEC 60601-1-2, IEC 60801-2,3,4,5, CISPR 11 or IEC 61000-4-2,3,4,5);

or

Test results which guarantee a similar level of protection;

or

Justification for why this information is unnecessary (e.g., due to device design or working conditions).

Disinfection of Device (Sterilization):

All *in vivo* devices should be disinfected to limit cross-contamination and patient-to-patient transmission of disease.

Reusable components

If the device is patient contacting, discuss the methods used to ensure that there is no potential for patient-to-patient transmission of disease. All devices intended for use *in vivo* should undergo reprocessing commensurate with their use and potential for patient contamination. Devices that contact/enter a sterile tissue must be sterilized before use. Devices which contact mucosal membranes that are not intact (or may become compromised during the procedure) should be

sterilized or high level disinfection ("semi critical" devices). Sterilization is preferred, but a high level disinfection may be adequate for this category of devices if sterilization is not possible.

Describe the methods used to validate the recommended reprocessing procedure. 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.

Single-use components

If the single use component is supplied sterile or disinfected, describe the method of sterilization or disinfecting:

1. Provide the sterilization method;
2. Provide the sterility assurance level;
3. Identify the method used to validate the sterilization/disinfection procedures. If the method is a standard, well-recognized method, simply reference the method.
4. Provide a description of the packaging system that will maintain sterility / disinfection.
5. 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.

5 SUMMARY OF ALL PRIOR BENCH TESTING (*IN VITRO* AND ANIMAL) INVESTIGATIONS

Provide a complete description of all *in vitro* and animal testing. This should include:

1 Justification for choice of model
2 Comparison of the model used in the study to that proposed to be used in humans
3 Test protocols and methods
4 Results (including samples of raw data)
5 Conclusions
6 Good Laboratory Practices (GLPs), 21 CFR Part 50.

Note: FDA is willing to review preclinical test data showing initial safety and functional performance through the pre-IDE or IDE pathway, depending on the determination of significant risk.

6 CLINICAL TESTING - GENERAL

A plan for clinical testing needs to include a pilot or feasibility phase I study and safety and effectiveness phase II studies. The purpose of the pilot/feasibility phase I study is to demonstrate the safety of the device and optimize prformance through testing in limited number of women. This phase involves testing and development of the algorithm, workability of the device, repeatability of the device, training needed for use of the device, and preliminary effectiveness of the device in a limited number of patients, and to determine the device cutoffs to be used in the Phase II clinical trial.

The phase II studies are designed to obtain the safety and effectiveness data necessary to support a Premarket Approval (PMA) submission as well as to validate device cutoffs.

Previous Clinical Testing

Provide the following information about all prior clinical investigations involving the device:

- Complete bibliography and include copies of the important references.
- Provide summary of all published and unpublished data, including performance results, definitions of key variables, patient inclusion/exclusion criteria, and other information that might help to establish relevancy to the current clinical trial.
- Complete discussion of all known adverse events or device failures

Common Elements for All Clinical Studies Including the Pilot / Feasibility Phase I Study and Safety and Effectiveness Phase II Studies

The following information should be included regardless of the indications for use:

- The justification for all the actions the sponsor plans to take in the written protocols for the different indications of use, comparing the *in-vivo* device to cervical/vaginal cytology, colposcopy and/ or biopsies, etc.
- The recommended sequence for performing each diagnostic procedure, i.e., cervical/vaginal cytology, the *in vivo* device, colposcopy, etc.
- The time interval between each procedure during both the preliminary pilot / feasibility study and the full clinical study.
- The description of the cervical/vaginal clinical examination. Note: sponsors should provide the following:

  ⇒ The type of cervical/vaginal cytology method used, such as liquid-based collection versus conventional direct smear.
  ⇒ Documentation that the personnel conducting the studies are comparable in education and training to the intended users of the device.

⇒ Record of colposcopic appearance, including location of transformation zone.

⇒ Documentation and justification for the sequence in which the *in vivo* device, cervical/vaginal cytology and colposcopy will be used.

Selection of Study Subjects

The range of patient characteristics selected for inclusion and exclusion into the clinical studies should support all of the intended uses claimed in labeling of the device. Subgroups may include, but are not limited to, the following factors:

- Age
- Premenopausal /menopausal
- Menstruating/non-menstruating, (cycle phase)
- Parity
- Pregnant/non-pregnant (exclude pregnant women from feasibility study)
- Previous cervical surgical procedures that might disturb cervical anatomy
- Other gynecological conditions including but not limited to inflammatory conditions, infection, polyps, bleeding, different locations of transformation zone, etc.
- Previous radiation therapy
- Oral contraceptives and other hormonal therapy
- Medications
- Immunosuppression

Informed Consent

Provide copies of the informed consent forms that will be used during the study. You may consult the "Investigational Device Exemption Manual," available from FDA's Division of Small Manufacturer Assistance, for additional guidance on the necessary elements of informed consent.

User Training

This section should include the educational level and training requirements for the intended user, the training duration, who will provide the training, and need for certification for use of device, etc. The clinical studies should specify the minimum education and training necessary for the clinician to use the device.

Phase I Clinical Study - Pilot/Feasibility Study for Preliminary Safety and Effectiveness Data

Objective

The purpose of the pilot/feasibility clinical study is to determine the safety and preliminary effectiveness of the device in a limited number of patients. Pilot/ feasibility studies should validate device performance, including the ability to detect cervical cancer and its precursor lesions reliably. The pilot study should also provide some estimated device effectiveness that may be used for the sample size calculations in the Premarket Approval study.

Pilot/feasibility clinical studies should resolve the following safety and effectiveness concerns:

a) Potential effect of *in vivo* device on cervix:

Colposcopy should be performed first, *without acetic acid*, to document the physical appearance of the cervix. Next, the sensor should be applied to the patient. Finally, a second colposcopy, *without acetic acid*, should be done to detect any device-induced trauma to the cervix. Diagnostic results from the sensor and colposcopy should be compared. (This assumes that the sensor is to be used before application of any acetic acid. If the sponsor intends for the sensor to be used without regard to application of acetic acid, then data should be provided to show reproducible results before and after the acid swab.)

b) Effects of *in vivo* device on sample:

If the device is to be used before obtaining a cervical/vaginal cytology sample, the potential effects on the cytology sample should be evaluated. To detect whether cells are removed by the device, the tip, or cervix-contacting part of the device, should be rinsed in liquid cytology collection media which could be evaluated cytologically for the presence of cellular material. Alternatively, a pilot study may randomly alternate the order of device and cytology collection, to determine whether the device adversely affects the cytology results.

c) Localization error:

If the *in vivo* device is intended to localize lesions, colpophotography or a similar technology should be used for documentation. The protocol should precisely describe how the clinician would determine that the device reading and the biopsy were taken from the exact same location. For example, if the device is used to localize lesions, the most precise

technology available for documentation would be computerized digital imaging rather than colpophotography. This method would allow exact coordinates to be determined for colposcopically derived biopsies to be compared with similarly obtained coordinates from the *in vivo* device imaging.

d) Protocol for Selection of Biopsies:

Directed cervical biopsies should be done based on the colposcopic examination, as defined in a written protocol. Directed cervical biopsy should follow the 'second' colposcopic exam. This should include the most abnormal site identified colposcopically. If the device is intended to localize a particular lesion, directed biopsy should be done at the site with the highest reading from the *in vivo* detection device, or at other sites with readings above the pre-determined threshold for *in vivo* device, if these sites were not previously identified as biopsy sites by colposcopy.

e) Protocol for Histopathologic Examination:

A written protocol should be defined for the histopathological examination of each of the colposcopy, and the *in vivo* device-directed biopsies. The examining pathologist should be masked to the method used to select the biopsies.

Phase II Clinical Study - Safety and Effectiveness

Overview

This section should discuss the safety and effectiveness study design to support the requested indication for the proposed *in vivo* detection device. Sponsors that plan to pursue combined indications for use should consider the issues addressed in each applicable section.

1 **Adjunct to the Cervical/Vaginal Cytology** - The *in vivo* detection device will be used in addition to cervical/vaginal cytology for primary screening of cervical cancer and its precursors.

2 **ASCUS Triage or Triage Following an Abnormal Cervical / Vaginal Cytology Test Result-** The *in vivo* device will be used to determine which patients with abnormal cervical/vaginal cytology screening test results are to be referred to colposcopy or LEEP.

3 **Localize Biopsy Sites** – The *in vivo* device will be used at the time of colposcopy as an adjunct to colposcopic examination to assist in the localization of biopsy sites.

4 **Primary Screening Device as an Alternative to Cervical / Vaginal Cytology** - The *in vivo* detection device will be used as a replacement for the cervical/ vaginal cytology as a primary screening tool.

Sponsor should quantify the improvement in sensitivity or specificity targeted as a goal and the 'clinically significant decrease' in the other measures targeted to be avoided. Quantification of the study hypothesis will facilitate the choosing of a sample size, as well as the ultimate determination of the success of the *in vivo* device in the clinical trial. For example, the sponsor might target an improvement in sensitivity of at least 5 percent, above the expected sensitivity of 85% without the *in vivo* device, while not reducing the specificity of the *in vivo* device by more than 3 percent.

For indications 1 and 4, a general guideline for clinical design would involve colposcopy of all women with cervical/vaginal cytology of ASCUS or above, or with *in vivo* device readings over the claimed threshold. A statistically appropriate proportion of cases that are negative by cervical/vaginal cytology and the *in vivo* device should also have colposcopy. Sensitivity analysis for the device should be based on histologically confirmed LSIL (CIN I) as well as HSIL (CIN II) and above.

The study designs presented here represent some possible approaches for demonstrating the safety and effectiveness of the *in vivo* device for the proposed indications for use. Alternate study designs and other indications for use will be considered by FDA on a case-by-case basis.

Indications for Use 1 - Adjunct to the Cervical / Vaginal Cytology

Intended Use

The *in vivo* detection device will be used in addition to the cervical/ vaginal cytology for primary screening for cervical cancer or its precursors. Specify if the *in vivo* device is to be used before or after the collection of the cervical/vaginal cytology specimen. The *in vivo* device may provide immediate diagnostic information that may be used to triage patient before cytological results are available.

Description of patient population

All women age 18 or above

Inclusion / Exclusion Criteria

The types of patients selected for inclusion and exclusion into the clinical study should support the intended use and indications for use claimed in the labeling of the device. (See Common Elements above page 12.)

Investigational Plan

Hypothesis

The sponsor may target an improvement in either sensitivity or specificity, as long as there is no substantial sacrifice of performance in terms of the other measure of performance.

Factors to Consider in Designing the Clinical Study

- Masking (blinding) of the test results: All patients should be examined by cervical/vaginal cytology and the *in vivo* detection device during the primary screening examination. The results of the *in vivo* detection device are withheld from the clinician until the results of the cervical/vaginal cytology are available. Also, the pathologist reading the cervical/vaginal cytology smear should be masked to the results of the in-vivo device.

- Criteria for Referral to Colposcopy: After the results of the cervical/vaginal cytology are received, if the test result from either the cervical/vaginal cytology or the device is positive, the patient should be scheduled for colposcopy. In addition, colposcopy should be performed on a certain proportion of the patients who are negative by both cytology and the new *in vivo* device to provide an estimate of the false negative results of cytology and the new *in vivo* device (false negative fraction or proportion). The study sponsor should justify the cytological criteria that

will be used to refer the patient to colposcopy for the cervical/vaginal cytology and the threshold criteria to be used for referral to colposcopy based on the results from the *in vivo* detection device.

- Time Interval Between Cytology and Colposcopy: The time interval between screening and colposcopy should be as short as possible, ideally less than 4 weeks.

- Choosing Where to Biopsy the Cervix: Directed biopsy should be done based on the usual criteria for colposcopic examination, as defined in the written protocol.

- Histopathologic Requirements: A written protocol should be defined for the histopathological examination of each of the directed biopsies, and the examining pathologist should be masked as to the clinical method used to triage to colposcopy.

- Resolution of Discrepant Results: If there are discrepant (discordant) results between cytology (HSIL+) and histopathology, then repeat colposcopy and biopsy should be performed. The histopathologic results should be entered into the study results and analysis.

Number of Study Subjects

- Sample size calculations should be based on appropriate statistical techniques and a quantified study hypothesis. The clinically significant differences to be detected should be part of the study hypothesis.

- Sample size should be chosen to confer adequate power to detect a statistically significant difference between cervical/vaginal cytology alone, and the combination of cervical/vaginal cytology plus the *in vivo* detection device for detection of biopsy-proven LSIL (CIN 1) and HSIL+ (CIN 2, CIN 3, Cancer).

- No fewer than 3 clinical sites should be used.

Data Analysis

- Compare specificity and sensitivity between cervical/vaginal cytology alone and the combination of cervical/vaginal cytology plus *in vivo* detection device for detection of biopsy-proven LSIL (CIN 1) and HSIL+ (CIN 2, CIN 3, Cancer). 'Sensitivity' is the percentage of patients with an abnormal histopathologic diagnosis who were found abnormal by the diagnostic test relative to its cutoff in the clinical trial, while 'specificity' is the percentage diagnosed *not* abnormal who were found *not* abnormal by

the test. The method to establish a final histopathologic diagnosis should not include the *in vivo* device results as an element in the decision, since in the clinical trial its effectiveness has not been proven.

- The percentage of patients referred to colposcopy may be considered as a proxy to determine any clinically significant loss of specificity for the *in vivo* device.

- Justify whether the final histopathologic diagnosis will be performed by one independent expert histopathologist, consensus from a panel of independent expert pathologists, or side by side adjudication from a panel of expert pathologists, etc.

- Pooling of performance results should be justified based on statistical assessment of homogeneity across clinical sites, using the clinical trial data, subject to the caveat that the degree of variation in performance, even if statistically significant, may not be significant from a clinical perspective. Lack of homogeneity would dictate that the labeling should give performance results by clinic, and that the pooled results should be interpreted with caution.

Indications for Use 2 - ASCUS Triage or Triage Following an Abnormal Cervical/Vaginal Cytology Test Result

Intended Use

The *in vivo* detection device will be used to determine which patients with abnormal cervical/vaginal cytology screening test results are to be referred to colposcopy or LEEP.

Description of patient population

Women with an abnormal ASCUS or higher screening test within the past four weeks are preferred. The manufacturer should justify any other time frame.

Inclusion / Exclusion Criteria

The types of patients selected for inclusion and exclusion into the clinical study should support the intended uses claimed in the proposed labeling of the device. Subgroups should be included, depending on indication to use, representing the spectrum of cervical changes found in women. (See Common Elements above)

Investigational Plan

Hypothesis

The *in vivo* detection device can be used to triage patients into appropriate treatment or follow-up as defined under intended use. The sponsor may target an improvement in either sensitivity or specificity, as long as there is no substantial sacrifice of performance in terms of the other measure of performance.

Factors to Consider in Designing the Clinical Study

- Cytological Criteria for Inclusion Into Study: Patients must have had an abnormal screening cervical / vaginal cytology test as the entry point. The study sponsor should justify the cytological diagnosis used to refer patients for device evaluation.

- Time Interval From Last Screening Test: Patients should have had an ASCUS or higher abnormal cervical/vaginal cytology screening test within the past 4 weeks.

- Criteria for Directed Biopsy: Directed biopsies should be done as defined in a written protocol, and should include the most abnormal sites identified colposcopically, as well as the abnormal sites identified by the *in vivo* detection device, if the *in vivo* device is intended to localize a particular lesion.

- Protocol for Histopathologic Examination: A written protocol should be defined for the histopathological examination for each of the directed biopsies, and the examining pathologist should be masked to the clinical method used to select the biopsies.

Number of study subjects

- Sample size calculations should be based on appropriate statistical techniques and a quantified study hypothesis. The clinically significant differences to be detected should be part of the study hypothesis.

- No fewer than 3 clinical sites should be used.

Data Analysis

- The sensitivity of the *in vivo* detection device to identify all of the patients with LSIL lesions or HSIL+ lesions should be calculated. 'Sensitivity' is

the percentage of patients with an abnormal histopathologic diagnosis who were found abnormal by the diagnostic test relative to its cutoff in the clinical trial. The method to establish a final histopathologic diagnosis should not include the *in vivo* device results as an element in the decision, since in the clinical trial its effectiveness has not been proven.

- The percentage of patients referred to colposcopy may be considered as a proxy to determine any clinically significant loss of specificity for the *in vivo* device.

- Justify whether the final histopathologic diagnosis will be performed by one independent expert histopathologist, a consensus from a panel of independent expert pathologists, or side by side adjudication from a panel of expert pathologists, etc.

- Pooling of performance results should be justified based on statistical assessment of homogeneity across clinical sites, using the clinical trial data, subject to the caveat that the degree of variation in performance, even if statistically significant, may not be significant from a clinical perspective. Lack of homogeneity would dictate that the labeling should give performance results by clinic, and that the pooled results should be interpreted with caution.

Intended Use 3 - Localize Biopsy Sites

Intended Use

The *in vivo* detection device will be used at colposcopy to help localize sites for biopsy.

Description of patient population

Women with abnormal cervical / vaginal cytology referred for colposcopy.

Inclusion / Exclusion criteria

Women who are candidates for colposcopy.
Same as for Indication 2.

Investigational Plan

Hypothesis

The ability of the *in vivo* device to select the most histopathologically abnormal areas for biopsies is as good as, or better than, colposcopy.

Factors to Consider in Designing the Clinical Study

- Cytological Criteria for Inclusion Into Study: Patients must have had an abnormal screening cervical / vaginal cytology test as the entry point. The study sponsor should justify the cytological criteria used to refer patients for colposcopy.

- Time Interval From Last Screening Test: Patients should have had an ASCUS or higher abnormal cervical/vaginal cytology screening test within the past 4 weeks.

- Documentation of the Appearance and Location of Cervical Biopsies: Biopsy sites should be identified by the *in vivo* device, without reference to the colposcopic examination. Colpophotography or a similar technology should be used for documentation of the colposcopy findings. A method such as computerized digital imaging should be considered to document abnormal sites identified by *in vivo* device readings and colposcopy. The protocol should describe precisely how the clinician would determine that the *in vivo* device reading and the biopsy were taken from the exact same location.

- Histopathologic Criteria: A written protocol should define the criteria for histopathological examination of the directed biopsies. Ensure that the pathologist is masked to the clinical method used to select the biopsy sites.

Number of study subjects

- Sample size calculations should be based on appropriate statistical techniques and a quantified study hypothesis. The clinically significant differences to be detected should be part of the study hypothesis.

- No fewer than 3 clinical sites should be used.

Data Analysis

- Compare biopsy sites selected by colposcopy with sites selected by readings of *in vivo* device and the resulting histopathology.
- The sensitivity and specificity of the *in vivo* detection device to identify biopsy sites of LSIL (CIN 1) lesions or HSIL+ (CIN 2, CIN 3, Cancer) lesions should be calculated.

- Justify whether the final histopathologic diagnosis will be performed by one independent expert histopathologist, a consensus from a panel of independent expert pathologists, or side by side adjudication from a panel of expert pathologists, etc.

- Pooling of performance results should be justified based on statistical assessment of homogeneity across clinical sites, using the clinical trial data, subject to the caveat that the degree of variation in performance, even if statistically significant, may not be significant from a clinical perspective. Lack of homogeneity would dictate that the labeling should give performance results by clinic, and that the pooled results should be interpreted with caution.

Intended Use 4 - Primary Screening Device as an Alternative to Cervical/Vaginal Cytology

Intended Use

The *in vivo* detection device may be used as an alternative to the cervical/vaginal cytology as a primary screening device.

The assessment of the safety and effectiveness of the *in vivo* device will be based on the performance characteristics of the new *in vivo* device in comparison to cervical/vaginal cytology. The potential advantage of having immediate diagnostic information with the *in vivo* device should be balanced against any decreases in sensitivity and/or specificity in comparison with cervical/vaginal cytology and with considerations of different clinical settings for the application of the *in vivo* device.

All factors listed under indication for use 1-As an adjunct to the Cervical/ Vaginal Cytology would apply for this intended use.

Description of patient population

All women age 18 or above

Inclusion / Exclusion Criteria

Same as indication 1.

Investigational Plan

Hypothesis

Any device that is intended to replace primary screening by cervical/vaginal cytology will require valid scientific evidence that

documents the *in vivo* device is equal or superior to the cervical/vaginal cytology, with a high degree of confidence for sensitivity and specificity, and provides the reasonable assurance of safety and effectiveness for all of the clinical indications claims for the in vivo device.

The new device results should be accurate and precise over time when used in the intended sites of use.

Factors to Consider in Designing Clinical Study

- Subgroups of women at higher risk for new indication for use: Because the device will be used as a primary screening tool, the sponsor should demonstrate appropriate levels of safety and effectiveness in all possible sub-groups of women. A particular concern would be if the indications include older women or others with a transformation zone that may be obscured within the endocervical canal.

- Detection of glandular lesions: The sponsor needs to consider detection of glandular lesions and adenocarcinoma. If the endocervix can not be visualized by the device, there should be a limitation statement in the intended use statement that the *in vivo* device may not be used to detect carcinoma or its precursor lesions within the endocervix.

- Criteria for Referral to Colposcopy: After the results of the cervical/vaginal cytology are received, if the test result from either the cervical/vaginal cytology or the device is positive, the patient should be scheduled for colposcopy. In addition, colposcopy should be performed on a certain proportion of the patients who are negative by both cytology and the new *in vivo* device to provide an estimate of the false negative results of cytology and from the new *in vivo* device (false negative fraction or proportion). The study sponsor should justify the cytological criteria that will be used to refer the patient to colposcopy for the cervical/vaginal cytology and the threshold criteria to be used for referral to colposcopy based on the results from the *in vivo* detection device.

- FDA Advisory Panel input: A meeting of FDA's OB/GYN Advisory Panel, (July 14-15, 1997) recommended that a clinical study for this new indication for the *in vivo* device should include a comparison of the new *in vivo* device with cervical/vaginal cytology in prospective patient population studies.

Number of study subjects

- Sample size calculations should be based on appropriate statistical

techniques and a quantified study hypothesis. The clinically significant differences to be detected should be part of the study hypothesis.

- Sample size should be chosen to confer adequate power to detect any statistically significant difference between performance of cervical/vaginal cytology (PAP smear results), and the *in vivo* detection device for detection of biopsy-proven LSIL (CIN 1) and HSIL+ (CIN 2, CIN 3, Cancer).

- No fewer than 3 clinical sites should be used.

Data Analysis

- Compare specificity and sensitivity between cervical/vaginal cytology and the *in vivo* detection device for detection of biopsy-proven LSIL (CIN 1) and HSIL+ (CIN 2, CIN 3, Cancer). 'Sensitivity' is the percentage of patients with an abnormal histopathologic diagnosis who were found abnormal by the diagnostic test relative to its cutoff in the clinical trial, while 'specificity' is the percentage diagnosed *not* abnormal who were found *not* abnormal by the test. The method to establish a final histopathologic diagnosis should not include the *in vivo* device results as an element in the decision, since in the clinical trial its effectiveness has not been proven.

- The percentage of patients referred to colposcopy may be considered as a proxy to determine any clinically significant loss of specificity for the *in vivo* device.

- Justify whether the final histopathologic diagnosis will be performed by one independent expert histopathologist, a consensus from a panel of independent expert pathologists, or side by side adjudication from a panel of expert pathologists, etc.

- Pooling of performance results should be justified based on statistical assessment of homogeneity across clinical sites, using the clinical trial data, subject to the caveat that the degree of variation in performance, even if statistically significant, may not be significant from a clinical perspective. Lack of homogeneity would dictate that the labeling should give performance results by clinic, and that the pooled results should be interpreted with caution.

7 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 judgment about the Quality Systems used in the manufacture of the device.

8 OTHER REQUIRED INFORMATION (21 CFR PART 812.20)

Commercialization.

Specify whether the device services will be charged to the patients during the clinical study. If so, explain why this does not constitute commercialization. 21 CFR Part 812.20 (8) " If the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device."

Environmental Impact.

Provide either:

- An environmental impact assessment describing the potential environmental impact from manufacturing and investigating the device;
  or
- A claim for categorical exclusion from the requirement, in accordance with 21 CFR Part 25.24.

9 REFERENCES

FDA Related 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.

1. Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices 5/1/95 (G95-1) = 10993 - Biocompatibility reference
   http://www.fda.gov/cdrh/g951.html
2. General Principles of Software Validation, Draft Guidance
   http://www.fda.gov/cdrh/comp/swareval.html
3. Guidance for Off-the-Shelf Software Use in Medical Devices – Draft Released 8/17/98
   http://www.fda.gov/cdrh/ode/otssguid.pdf
4. Electromagnetic Compatibility and Interference - multiple references
   http://www.fda.gov/cdrh/emc/index.html
5. Guidance Document for Washers and Washer-Disinfectors Intended for Processing Reusable Medical devices.
   http://www.fda.gov/cdrh/ode/washdsnf.html
6. Investigational Devices Exemption Manual
   http://www.fda.gov/cdrh/manual/idemanul.html
7. DCLD Guidance Document: *Points to Consider: Cervical Cytology Devices*, Version 7/25/94, FOD DOC 968
   http://www.fda.gov/cdrh/ode/968.pdf
8. Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.
   http://www.fda.gov/cdrh/ode/57.html
9. Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities.
   http://www.fda.gov/cdrh/ode/1198.html
10. Premarket Approval Manual
    http://www.fda.gov/cdrh/manual/510kprt1.html

Applicable Consensus Standards

The following are voluntary industry consensus standards that may be applicable to one or more of these electrooptical sensor systems:

1. IEC 60601-1-1-1, Medical Electrical Equipment, Part 1: General Requirements for Safety, 1. Collateral Standard: Safety Requirements for Medical Electrical Systems, 1992.
2. IEC 60601-1-2, Medical Electrcal Equipment, Part 1: General Requirements for Safety, 2. Collateral Standard: Electromagnetic Compatibility – Requirements and Tests, 1993.
3. Underwriters Laboratories, http://www.ul.com
4. ISO 10993, Biological Evaluation of Medical Devices Part 1: "Evaluation and Testing".
5. American Conference of Governmental Industrial Hygienists, Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices 1996 (American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, 1996).
6. ANSI (1993) Safe use of Lasers, standard Z-136.1-1993. American National Standards Institute, Laser Institute of America, Orlando, Fl.

Clinical References

1. Brookner C.K., Agarwal A., Trujillo E.V., Mitchell.M.F., and Richards-Kortum R.R. Safety analysis: Relative risks of ultraviolet exposure from fluorescence spectroscopy and colposcopy are comparable, Photochem. and Photobiol., 1997, 56(6): 1020-1025.
2. Burk l., Niloff J., Kobelin M., Abu-Jawdeh G., Zelenchuk A., and Modell M. Use of Autofluorescence of Cells to Evaluate Cervical Neoplasia, Journal of Gynecologic Techniques 1996; 2, 4: 187-190.
3. Coppleson M., Reid, B.L., Skladnev, V.N., and Dalrymple, J.C. An electronic approach to the detection of precancer and cancer of the uterine cervix: a preliminary evaluation of the Polarprobe®. Int J Gynecol Cancer 1994; 4: 79 - 83.
4. Eddy D.M., Screening for cervical cancer. Annal Intern Med 1990; 113: 214-26.
5. Fahey MT, Irwig Les, Macaskill P. Meta-analysis of Pap test accuracy. Am J Epidemiol 1995; 141: 680-9.
6. Ho GYF, Bierman R, Beardsley L, Chang C.J., Burk R.D. Natural history of cervicovaginal papillomavirus infection in young women. NEJM 1998; 338:423-8.
7. Koss LG. The Papanicolaou test for cervical cancer detection: A triumph and a tragedy. JAMA 1989; 261:737-43.
8. Kurman RJ, Solomon D. The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses. New York: Springer-Verlag, 1994.

9. Mahadevan, A., Mitchell, M.F., Thomsen, S., Silva, E., and Richard-Kortum, R.R. Study of the fluorescence properties of normal and neoplastic human cervical tissue. Lasers Surg. Med. 1993, 13, 647 -655.
10. NCCLS. Papanicolaou Technique. Approved Guideline. NCCLS Document GP 15-A. NCCLS, Wayne, Pennsylvania, 1994.
11. National Cancer Institute Workshop. The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses. JAMA 1989;262:931-4.
12. National Cancer Institute Workshop. The 1991 Bethesda System for reporting cervical/vaginal cytologic diagnoses. Acta Cytol 1993;37:115-24.
13. Intersociety Working Group. Proposed guidelines for primary screening instruments for gynecologic cytology. Intersociety Working Group for Cytology Technologies. Diagn Cytopathol. 1998; 18: 371-6.
14. Intersociety Working Group. Proposed guidelines for evaluating secondary screening (rescreening) instruments for gynecologic cytology. Intersociety Working Group for Cytology Technologies. Diagn Cytopathol. 1998; 19: 468-71.
15. Ramanujan N., Mitchell, M.F., Mahadeven, A., Thomsen S., Malpica A., Wright T., Atkinson N., and Richard-Kortum, R.R. Spectroscopic diagnosis of cervical intraepithelial neoplasia (CIN) in vivo using laser induced fluorescence spectra at multiple excitation wavelength. Lasers Surg Med 1996, 19: 63-74.
16. Renshaw A.A., Dean B.R., Cibas E.S. Receiver operating characteristic curves for analysis of the results of cervicovaginal smears. A useful quality improvement tool. Arch Pathol Lab Med. 1997; 121: 968-75.