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 Female Barrier Contraceptive Devices Also Intended to Prevent Sexually Transmitted Diseases

April 4, 1990

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Preface

Over the past several years, the Food and Drug Administration (FDA) has followed with alarm the increase in prevalence of sexually transmitted diseases (STDs) in the United States, especially Acquired Immunodeficiency Syndrome (AIDS). Aside from sexual abstinence or a monogamous sexual relationship with an uninfected partner, most responsible clinicians believe that barrier contraception may be the only way to avoid STDs. FDA recognizes the difficulty in developing any contraceptive device, with the necessary clinical studies demonstrating safety and effectiveness, as conventionally defined. The guidelines laid out in this document are FDA's attempt, in the interest of public health, to provide manufacturers and researchers a streamlined study and evaluation approach for bringing important barrier contraceptive devices to market. Such devices must meet certain design criteria, and labeling for these devices must highlight the limitations of the safety and effectiveness data; but, overall, FDA believes that this approach will lead to an improved public health with respect to STDs.

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Introduction

These guidelines address the preclinical and clinical testing of female barrier contraceptive devices also intended to prevent transmission of sexually transmitted diseases (STDs), including Acquired Immunodeficiency Syndrome (AIDS). The guidelines were developed on August 25, 1989, at an open public meeting of the Obstetrics-Gynecology Devices Panel (the Panel) as a collaborative effort of experts from the Food and Drug Administration (FDA), the National Institute of Child Health and Human Development (NICHD), the Centers for Disease Control (CDC), and the Panel, involving substantial interactive dialogue with the public audience, as well.

Because of the profound detrimental effect of Human Immunodeficiency Virus (HIV) and AIDS on the public health and the need for such devices in the marketplace, CDRH prepared these guidelines to expedite device study and evaluation. These guidelines do not apply to barrier contraceptive devices without demonstrated potential to prevent transmission of STDs.

It is important to note that the barrier performance of the device, with respect to bacteria and viruses, must be established through adequate laboratory studies. Test methodology selected for this purpose should specify appropriate test conditions and be sufficiently sensitive to test STD-sized particles of interest. For these guidelines to be applicable, the device must also have been demonstrated to stay in place during use. **MANUFACTURERS ARE STRONGLY ENCOURAGED TO CONSULT WITH FDA's OFFICE OF DEVICE EVALUATION REGARDING THE APPLICABILITY OF THESE GUIDELINES TO THEIR OWN SPECIFIC PRODUCT.**

These guidelines are general because of the anticipated diversity of such devices. A manufacturer should develop study protocols specific to its device with the help of these guidelines. FDA's Premarket Approval Application (PMA) Manual (HHS Publication FDA 87-4214) should be consulted for overall guidance in the preparation of a PMA. During the PMA review process, FDA will evaluate the study protocol(s) for individual contraceptive devices on a case-by-case basis.

Because of the extreme difficulty in studying effects on STD rates in a clinical trial, the guidelines designate pregnancy as a surrogate study endpoint for demonstrating the device's effectiveness to prevent transmission of STDs. A key feature of these guidelines is the elimination of the requirement for a randomized controlled clinical trial to compare the performance of the new device to that of an established barrier contraceptive device in a concurrent control group. This is coupled with requirements for a strengthened feasibility study (Phase I) with emphasis on health risks and device displacement during use, followed by the non-randomized clinical trial (Phase II). The manufacturer must compare the results from this Phase II study to appropriate historical controls.

In summary, the material(s) and design of the new barrier contraceptive device should be thoroughly studied prior to beginning any clinical studies. Results from the clinical studies must support the safety and effectiveness of the new barrier contraceptive device, i.e., its risks or undesirable side-effects and its effectiveness in preventing pregnancy and transmission of STDs, leading ultimately to a risk-benefit assessment.

I. PRECLINICAL STUDIES

Preclinical studies are intended to identify the appropriate chemical, physical, design, and toxicological characteristics of the device that can be determined in laboratory studies and animal testing. This data should be submitted in the application for investigational device exemptions (IDE) to conduct clinical trials. Such testing should demonstrate the barrier performance of the device, with respect to STD microorganisms.

A. Description of Device

The applicant should provide detailed drawings and descriptions of the device. PMA applicants will be expected to make prototype, pre-production, and production device samples available to FDA for evaluation. The physical characteristics of the device should be detailed. The rationale for the device design should be stated in the light of the relevant literature or based upon sound theoretical reasoning.

A full description of the device should also be given in the device labeling. (See Section V - Labeling.)

The following design characteristics should be fully described:

1. shape and dimensions, including surface areas;

2. presence of projections, if any;

3. inserter design, including physical characteristics, insertion procedures, and any anticipated difficulties, if applicable; (If the device does not have an inserter, describe how the device is inserted, including any anticipated difficulties.) and

4. removal procedures and any anticipated difficulties.

B. Physical Properties

Appropriate engineering tests should be performed and the results considered relative to the device's mechanical and chemical properties, as well as to its design characteristics:

1. details of mixing, forming, curing, including the materials and sources employed and their percentage composition;

2. uniformity of components in the completed devices and procedures for quality control;

3. uniformity and texture of the device surface, as determined by surface scanning electron microscopy (SEM) or other appropriate methods;

4. tensile strength, tear strength, elasticity, and other measures

of the flexural characteristics of the device and its component materials, as well as vulnerability to puncture; and

5. material standards, if applicable.

Device labeling should include important findings from the physical testing, e.g., susceptibility to tearing or puncture (by fingernails, inserter, etc.), storage conditions, etc. (See Section V - Labeling.)

C. **Stability**

Physical and chemical properties of the device should be studied for prolonged exposure to the intended biological environment. Physical and chemical properties of the device may be altered by prolonged exposure to lubricants, or by the effects of transit and storage. Studies should be designed to support the use of the device in its intended biological environment, with lubricants or other agents, if appropriate. Testing should support the shelf-life claimed for the device.

D. **Toxicity**

The biocompatibility of device materials should be evaluated by appropriate in vitro and in vivo toxicological studies. The Tripartite Biocompatibility for Medical Devices Guidance may be useful for selecting the appropriate types of tests.

E. **Barrier Properties**

It is essential that the device under study be an effective physical barrier to bacterial and viral STD agents. Barrier performance of the device can be demonstrated by using test particles (e.g., microspheres, radio-labeled tracers, viruses, etc.) less than or equal to 42 nm in diameter, the size of the smallest known STD micro-organism (i.e., the hepatitis-B virus).

FDA encourages the development of new test protocols to demonstrate barrier performance. Given below are necessary considerations of a testing approach.

Under test conditions that simulate actual use, compare the new barrier device to an established (reference) device, such as the latex (rubber) condom. Demonstrate that the barrier performance of the new device is as good or better than that of the reference device.

Justify any test conditions that differ from actual use conditions and which may affect the comparison of barrier performance. Conditions which may be important include temperature, pH, viscosity, the surface tension of the fluid and the wetting angle of the barrier, physical and chemical properties of the test solutes, as well as other testing

conditions, such as the magnitude of applied pressure (steady or transient), barrier membrane stress or deformation, etc.

Test methodology must be sufficiently sensitive to evaluate the permeability of the reference device, particularly with respect to the size of the test particle, as stated above, and sufficient numbers of devices of each type should be tested to provide a statistically significant comparison.

Before choosing any barrier test method, you should consult with FDA's Office of Device Evaluation (Raju G. Kammula, D.V.M., Ph.D., at 301-427-1180) on whether the selected test method is scientifically sound in order to support the premarket approval of the device.

II. CLINICAL STUDIES

Before beginning clinical studies, all preclinical studies should be completed. An application for an investigational device exemption (IDE), per 21 CFR 812, should be submitted to FDA. FDA's IDE Manual (HHS Publication FDA 86-4159) should be consulted for overall guidance in the preparation of an IDE application. Patient informed consent must contain all required elements, per 21 CFR Part 50.25, including information on discontinuing use of the device and the study follow-up procedures.

A. Feasibility Study (Phase I)

1. Objectives

   Phase I studies are done to determine the feasibility, acceptability, fit, size, etc., and safety of the device. These studies should evaluate the following:

   a. potential adverse effects, including (i) mucosal irritation and sensitization, (ii) microbial flora of the vagina, cervix, and device, (iii) vaginal and cervical cytology, (iv) trauma, (v) ulceration, (vi) urinary tract infection, (vii) bleeding, (viii) salpingitis, (ix) pain, and (x) discomfort;

   b. device wear-time and device displacement and/or expulsions (The device must remain in place for the intended duration.); and

   c. post-coital testing.

   Documentation should include Papanicolau (PAP) smears and cervical photographs. PAP smears should be evaluated at a single clinical laboratory in order to maintain consistency.

2. Study Subject Selection and Exclusion Criteria

   The study subject must be protected by using an effective, non-barrier, means of contraception (oral contraceptives, IUD, or tubal sterilization).

3. Investigator Selection Criteria

   An investigator must be knowledgeable about all types of contraception in general and experienced in managing patients who use barrier contraceptive methods. The investigator must be willing to monitor closely each study subject and maintain reasonable follow-up.

4. Study Size and Duration

   The study should include at least 50 female study subjects, with at least 10 coital episodes per subject, giving a total of 500 evaluable coital episodes.

5. Instructions for Use

At the Phase I study, it should also be demonstrated that the target population can follow printed instructions, especially if the device is to be marketed as an over-the-counter (OTC) product. That is, 1) how well does the target population properly use the device , and 2) how well does the target population understand other important messages, such as visually checking for defects, proper storage, etc. Particular effort should be made to demonstrate that patients with limited education and/or literacy can understand printed instructions for an OTC device or can understand a health care provider's instructions for a prescription device. Such studies should include well-constructed questionnaires, as well as clinical observations by health professional investigators. (See also Section II.B.5 - Instructions for Use.)

Consult with FDA's recent "GUIDANCE ON THE REVIEW OF INVESTIGATIONAL DEVICE EXEMPTIONS (IDE) APPLICATIONS FOR FEASIBILITY STUDIES".

B. **Safety and Effectiveness Study (Phase II)**

The Phase II study demonstrates safety, effectiveness and ease of use of the device. Because the requirement for a Phase III randomized controlled clinical trial was eliminated, increased emphasis is placed on the results of the Phase II study for all aspects of safety and effectiveness. This evaluation approach must compare the results of study of the new device to results from the study of an appropriate historical control group (e.g., cervical cap or diaphragm) with a comparable population profile accounting for relevant factors, such as age and socio-economic status. A manufacturer may obtain further information the acceptable use of an historical control group by contacting FDA's Office of Device Evaluation (Raju G. Kammula, D.V.M., Ph.D., at 301-427-1180).

1. Study Subject Selection Criteria

a. Study subjects must be between 18 and 40 years old and should not have a history of infertility or conditions that lead to infertility. Study subjects must agree not to use additional forms of contraception and must be willing to accept the potential risk of pregnancy.

b. Selection of study subjects should reflect the intended target population when the device is marketed. Types of patients that should be included:

i. previously gravid;
ii. nulligravid (must have an established normal menstrual pattern);
iii. current or previous barrier contraceptive users; (Note that if the device under investigation is very similar to the one the subject is using or previously

used, this may influence the study results.)
iv. non-barrier contraceptive users; and
v. never users of contraception (must have an established normal menstrual pattern).

c. Study subjects must be sexually active with at least 2-3 coital episodes weekly.

d. Study subjects must have had at least two normal consecutive menstrual cycles under the following circumstances:

i. after discontinuing hormonal contraceptives; or
ii. recently postpartum or postabortion.

2. Study Subject Exclusion Criteria

a. Study subjects who are pregnant, have a suspected pregnancy, or desire to become pregnant while participating in the study should be excluded from the study.

b. Study subjects who are unable to conform to the follow-up schedule or study subjects who anticipate moving away from the area within the study duration should be excluded from the study.

c. Study subjects who cannot be fitted with the device, or who are unable to understand instructions for use, or who are unable to correctly apply the device should be excluded from the study.

d. Study subjects with the following medical conditions should be excluded from the study:

i. a history of infection or surgery that might compromise fertility;
ii. a medical condition contraindicating pregnancy, such as diabetes or heart disease;
iii. undiagnosed vaginal bleeding;
iv. untreated abnormal PAP smear; or
v. cervical cytology equivalent to Class III or worse.

Data on study subjects using the device and later found to have one of the above conditions must be analyzed and reported separately. Such cases may not count towards the required total number of study subjects. (See Section II.B.6 - Statistical Evaluation, below.)

3. Investigator Selection Criteria

a. There should be at least two investigators conducting the studies at a minimum of two separate sites.

b. Each investigator shall contribute an equal number of study subjects to comprise a statistically valid sample.

c. An investigator must be knowledgeable about all types of contraception in general and experienced in managing patients who use barrier contraceptive methods. The investigator must be willing to closely monitor each study subject and maintain reasonable follow-up. The status of each patient must be determined on a monthly basis and significant events must be entered into a monthly report.

d. The investigator should use a 3-month "holding" period for data collection, after the designated study duration, to ascertain pregnancies and other events of interest that may have actually occurred during the duration of observed use, but not discovered by the patient or reported to the investigator during that time.

4. Study Size and Duration

The number of subjects should be sufficient to end up with at least 200 study subjects, contributing to a standard 12-month lifetable analysis. Depending upon monthly interval analysis, CDRH, on a case-by-case basis, may permit submission of a PMA application with a 6-month (or less) lifetable analysis. (See Section IV - Post Market Surveillance.)

5. Instructions for Use

Because the effectiveness of barrier contraceptive devices is so dependent upon proper use, Phase II studies must demonstrate, as an extension of the results from the Phase I studies, how well patients can understand printed instructions for an OTC device, or, for prescription devices, how well patients will understand the printed instructions and a health care provider's instructions. That is, similar to the Phase I studies, 1) how well does the target population properly use the device, and 2) how well does the target population understand other important messages, such as visually checking for defects, proper storage, etc. Particular effort should be made to demonstrate that patients with limited education and/or literacy can understand printed instructions for an over-the-counter (OTC) device, or can understand a health care provider's instructions for a prescription device. Such studies should include well-constructed questionnaires, as well as clinical observations by health professional investigators.

As stated, FDA recommends that PMA applicants conduct consumer field evaluations to determine a lay person's ability to properly use the device unassisted, following instructions in the labeling. This information should be submitted to FDA in the PMA application. Key features of such an evaluation are given below:

a. Lay users selected for the study should be of limited education and literacy. (Patient selection criteria should

be submitted to FDA with the study protocol and results.)

b. The number of subjects selected for testing should be sufficient to support statistically valid conclusions.

c. A simple questionnaire, provided to study participants, may be used to determine if the user understood the purpose of the device, the conditions for its use, and any limitations or special precautions. (The PMA should contain a sample of the questionnaire, as well as a tabulation of all questionnaire responses.) The study write-up should also contain the results of observations made by nurse investigators.

6. Statistical Evaluation

Statistical analyses of safety and effectiveness should be done via the multiple decrement life table method or other appropriate analytic models, to permit simultaneous statistical treatment of important outcome events, such as pregnancy, expulsion or displacement, infection, abnormal PAP smears, discontinuation for pain/bleeding/other medical reasons, and discontinuation for personal reasons (desired pregnancy or dissatisfaction). Analysis should be conducted at one month intervals to examine the data for trends. Appropriate actions, warnings, or precautions should be taken if the monthly analysis so warrants. A standard 12-month life table analysis should be performed, but CDRH may accept a PMA with a 6-month (or less) life table analysis, depending upon the results of the monthly interval analysis. The confidence interval should be provided for the final cumulative pregnancy rate.

The start time for an individual subject's participation in the study, for the purposes of follow-up and life table analysis, is the date of first coitus after the woman has received a supply of contraceptive devices. The stop time depends upon decisions made on important outcome events, such as those given above. Each patient who has not terminated device use or who has not been lost to follow-up should have the required number of months of observed use of the device prior to completion of the analysis (unless discontinued for reasons given above). At least 200 study subjects should be analyzed, but more may be required, as appropriate, depending on the statistical power of the study. Both net and gross life table rates should be presented.

7. Data Collection

Provide demographic data on each study subject, including age, race, and socioeconomic status. If feasible, data should be collected on respondent satisfaction with prior contraceptive methods, particularly barrier methods.

Important outcome events, such as pregnancy or infection,

should be accompanied with both the date of reporting and estimated date of occurrence, and not just the ordinal month in which they occurred. This additional data will permit estimates of the time lapse between occurrence and reporting of events, and will also permit, if necessary, use of more elaborate statistical analyses such as Cox regression models.

The following specific data should be recorded and analyzed to evaluate safety and effectiveness:

a. date of pregnancy (Correlate to items #i and/or #j below.);

b. date of infection, type, and method of diagnosis;

c. trauma to vagina, cervix, or penis;

d. PAP smear conversions and intake history (The same laboratory should be used for all PAP smears.);

e. discomfort;

f. pain;

g. any other reported adverse effects;

h. ease of insertion and removal;

i. device rupture, tear, or puncture;

j. displacement/expulsion during use: how frequently and when;

k. subject compliance with study protocol and instructions for device use; data should be collected on subject understanding of other key messages in the labeling, such as under what circumstances one's personal health care provider should be contacted;

l. device discontinuation

   i. discontinuation date, medical reasons (specify, e.g., allergy, infection, trauma, odor, itching, etc.);
   ii. discontinuation date, dissatisfaction with device (specify, e.g., inconvenient, uncomfortable, partner can feel it, subject can feel it, etc.); and
   iii. discontinuation date, personal reasons unrelated to device (specify, e.g., desire to become pregnant, putting off sterilization, move from geographical area, etc.)

m. Level of acceptability - study subject

n. Level of acceptability - partner(s)

III. GOOD MANUFACTURING PRACTICES (GMPs)

A description of Good Manufacturing Practices (GMPs) and quality assurance (QA) procedures for the device should be submitted in the premarket approval application. FDA will evaluate these procedures and practices for the specific device design. Refer to FDA's PMA Manual.

IV. POST MARKET SURVEILLANCE

During its review of the PMA, FDA may identify unforeseen device-related adverse effects. In this instance, FDA, in consultation with its advisory Panel, may impose post market surveillance requirements to obtain further information.

V. LABELING

Labeling must contain a complete description of the device based upon the findings from the preclinical and clinical studies. Because of the limited nature of the Phase I and Phase II studies for these devices, FDA will require full disclosure of the safety and effectiveness of the new barrier contraceptive devices, in the product labeling, with respect to all aspects, known and unknown, of device safety, effectiveness, and instructions for use. A limited product claim will also be necessary. FDA also recommends that the device manufacturer provide a toll-free telephone number or an address in the labeling for consumers to direct questions about device use or problems.

Manufacturers are encouraged to consult with FDA's manual, "Labeling: Regulatory Requirements for Medical Devices", (HHS Publication FDA 89-4203). It is also important, as stated earlier, that general labeling guidance given in FDA's PMA and IDE manuals be followed, as appropriate.

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