Testing guidance for Male Condoms Made from New Material (Non-Latex) (Text Only)

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PART A - INFORMATION FOR A NEW MATERIAL CONDOM 510(k) SUBMISSION FOR OBSTETRICS-GYNECOLOGY DEVICES BRANCH

This list of questions may not be all inclusive or specific for all non-latex materials.

A. General Information

1. Identify a predicate device and compare your device to the predicate device in terms of intended use, design, materials, specifications, and performance.

2. Provide copies of labels, labeling, and advertisements sufficient to describe the device, the intended uses and the directions for use.

B. Condom Sheath and Retention Mechanism Material(s)

Provide a detailed description of the condom materials for both the sheath and any retention
mechanism, to include the following:

1. name and manufacturer of the resin;

2. chemical composition and specifications of the sheath material(s) including molecular weight and molecular weight distribution;

3. the chemical composition and specifications for any retention ring material(s);

4. specifications for the raw materials and a description of the quality control testing performed;

5. molar ratio of component monomers for fabricating the material;

6. quantities of residual monomers and additives;

7. the chemical composition and specifications of any dusting agent(s); and

8. the lubricant(s) formulation, chemical composition of each ingredient, ingredient specifications, and quantity of lubricant applied the condom.

C. Manufacturing Processes

Provide the following information on the processes used to manufacture

the condom:

1. flow diagram for all aspects of condom manufacturing including points where in-line quality control testing is performed;

2. solvent based manufacturing process (blown, spun or dipped): OR See C.3.

    a) solvent(s);

    b) compounding additives including any color additive that may be added (If a color additive is used, provide its chemical composition, and identify its CAS number or its color index number and reference the specific color additive listing (21 CFR reference));

    c) solution handling processes;

    d) batch sizes of the dipping mixture;

    e) filtration of the stock materials;

    f) process control parameters, such as solution viscosity and temperature, system metrology, air handling specifications, particulate control, packaging process;

    g) the handling and/or reworking procedures of the product that fails any of the in-process quality control tests; and,

    h) a detailed description of the condom mandrels and condom manufacturing process including the rotational speed and angles (dipping process).

3. extrusion/film based manufacturing process (with seam welds):

    a) data from physical testing conducted on the extrusion/film material using appropriate sampling procedures (See Section E#2.);

    b) data on the quantities of residual solvent(s) and additives in the film;

c) compounding additives including any color additive that may be added (If a color additive is used, provide its chemical composition, and identify its CAS number or its color index number and reference the specific color additive listing (21 CFR reference));

d) film handling processes;

e) batch sizes of the extrusion film material;

f) process control parameters, such as temperature, system metrology, air handling specifications, particulate control, packaging process;

g) the handling and/or reworking procedures of the product that fails any of the in-process quality control tests; and,

h) a detailed description of the condom manufacturing process heat sealing procedures including dwell and temperature.

4. description of the procedures used to apply the retention ring;

5. description of the molecular weight and molecular weight distribution of the sheath material following the condom manufacturing processes;

6. data on the quantities of residual solvent(s) and additives in the final production condoms;

7. description of the procedure(s) to add dusting agent(s) and/or lubricant(s); and,

8. description of the procedures used to package the condom.

D. Material Toxicity

Provide the following material toxicology information:

1. summary of known toxicity data on all the monomers, additives, and

solvents utilized in manufacturing of the material(s) of the condom;

2. toxicity data on dusting agents and lubricants; and,

3. biocompatibility data on the finished (packaged, ready for distribution) product demonstrating that the condom material does not produce toxicity, including cytotoxicity, sensitization (polar and nonpolar extracts), mucosal irritation, acute systemic toxicity, mutagenicity, and implantation (90 day).

E. Finished Product

Please provide the following information on the finished condom:

1. a complete description of your device to include, material(s), design (e.g., length, width, thickness, reservoir tip, retention mechanism, etc.), and specifications (both chemical and physical);

2. data from the following physical testing conducted on the finished condom using appropriate sampling procedures and established performance limits and tolerances (Cross reference response with Section F):

   a) tensile strength;
   b) force at break;
   c) elongation;
   d) tear resistance and propagation;
   e) air burst volume;
   f) air burst pressure; and,
   g) water leakage.

3. data to demonstrate that the product's physical integrity is not compromised by short term exposure to body temperature, (e.g., tensile strength and elongation at 37 C).

F. Quality Control/Quality Assurance

1. detailed description of the test procedures used to

establish the quality of each condom lot or batch (Cross reference response with the flow diagram Section A#1), including:

a) when testing is performed during manufacturing processes (include sampling frequency);

b) a detailed description of any in-process testing procedures including a description of the in process testing machine, the machine's specifications, and operator's manual and a description of the testing machine's calibration procedures;

c) data to demonstrate the reliability, reproducibility and sensitivity of the in-process testing machine;

d) a description of the relationship between the in-process testing machines' calibration specifications to the product release testing specifications; and,

e) for each in-process or final release test, identify the acceptable quality level (AQL), the applicable sampling plan and inspection level for each test. Also, provide examples of the quality control procedures for a typical lot size by identifying appropriate acceptance and rejection values for each test conducted during quality control and quality assurance testing.

2. information on the water leakage test to include a detailed description of how the test is conducted including specifications and operating procedures, and calibration procedures; and,

3. information on the air burst test to include a detailed description of how the test is conducted including specifications and operating procedures, and calibration procedures.

G. Packaging

Provide specifications of the package material and sealing integrity.

H. Barrier Properties/Permeability: Viral Penetration Study

Provide data from in-vitro studies simulating actual use conditions to demonstrate the barrier properties of the condom with respect to the sexually transmitted disease (STD) organisms, and compare the barrier properties of new device to latex condom. (See attachment A, Guideline for Determining Barrier Properties of Condoms to Virus Penetration.)

I. Shelf-Life

Real-time and/or accelerated data is necessary to substantiate the claimed shelf-life. Testing should include but not be limited to testing of the condom and lubricant system after storage in the primary packaging system for materials compatibility and spermicidal effectiveness (if applicable), to include:

1. mechanical testing of finished condom (See Section E#2, above);

2. an analysis of chemical degradation byproducts and physical properties over time;

3. quantitative chemical analysis for the amount of spermicidal lubricant available over time (e.g., High Pressure Liquid Chromatography (HPLC));

4. bioassay of spermicidal efficacy using an accepted method to demonstrate the contraceptive effectiveness of the condom lubricant system (e.g., The International Planned Parenthood Federation Agreed Test for Total Spermicidal Power (IPPF Agreed Test). Also see the Vaginal Contraceptive Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Proposed Rulemaking (FR 82015-82049; 1980)).

PART B - CLINICAL TESTING GUIDANCE FOR NEW MATERIAL
MALE CONDOMS

Introduction

This section of the guidance addresses the clinical testing requirements for any new male latex or new material condom that differs significantly from conventional condoms in its design, materials, or technological characteristics. As with all new contraceptive devices, clinical trials of these condoms are considered significant risk device investigations under the investigational device exemptions (IDE) regulation, and an IDE application is required. An IDE application is not needed for preliminary studies where the study subject is protected by a back-up contraceptive, or if the contraceptive study is conducted in a post market setting.

New material male condoms offer a potential strategy to decrease the rate of unintended pregnancy and prevent the spread of sexually transmitted diseases (STDs) including HIV. This guidance for clinical testing of new condoms meets a recognized need to evaluate whether condoms of novel design or materials differ during use. This section of the guidance serves to provide a framework and context for clinical testing and to define recommended studies to evaluate new products. It is intended to be a working document, from which manufacturers initiate discussions with the Food and Drug Administration (FDA) staff regarding testing of new products. Alternate studies or changes in the suggested study design and analysis require justification. As more is learned about new materials from studies or other observations, the testing and evaluation of these products will evolve.

Before beginning clinical studies, all preclinical studies should be completed. All clinical studies should be conducted in accordance with 21 CFR Part 812, and FDA's investigational device exemptions (IDE) manual (HHS Publication FDA 86-4159) should be consulted for overall guidance.

From a premarket perspective, clinical testing of a new male condom should include an initial feasibility study to provide preliminary information on clinical performance (slippage and breakage), as well as

to rule out any immediate adverse effects, such as irritation. (See Section I, page 10.) A slippage and breakage study must be conducted and provide sufficient detail and sample size for a statistically valid comparative analysis of the study condom to a legally marketed condom. (See Section II, page 10.) A slippage and breakage study is necessary to assure that the properties of the new condom, such as physical attributes and device fit, are comparable.

Please note that early clinical studies of the condom, such as slippage and breakage studies, should generally be conducted in a low risk population defined as one of mutually monogamous couples who are using an effective non-barrier method of contraception (i.e., hormonal contraception, intrauterine device (IUD), or male/female sterilization). Alternatively, the study population could include couples at risk of pregnancy, but not planning pregnancy at the current time. These clinical studies of the device are generally not considered to be significant risk device investigations (as defined at 21 CFR 812.3(m)) if study subjects are not at significant risk of conception or of contracting an STD. As stated above, contraceptive efficacy trials, where study subjects are at risk for STDs and pregnancy, are generally considered to be significant risk device investigations. Please contact FDA if you have questions regarding the requirement for an IDE application.

Because there are no validated models to predict the contraceptive effectiveness of a new condom from other clinical performance such as breakage and slippage rates, a contraceptive effectiveness study is to be conducted. (See Section III, page 13.) The contraceptive effectiveness study should be designed, conducted, and analyzed to compare the pregnancy use-effectiveness, adverse events, and study discontinuation rates of the new condom to a legally marketed latex condom. STD screening tests may be offered, but not necessarily required.

Due to the current public health need for alternatives to latex condoms, the contraceptive efficacy trial may be conducted in a post-market setting. Under these circumstances, such investigations are exempt from the IDE regulations requirement for submitting an IDE application to the agency. To meet the exemption criteria, the product must be cleared beforehand, through the 510(k) review process, with satisfactory preclinical performance data and satisfactory clinical safety and slippage and breakage performance. Interim labeling while gathering

clinical efficacy data is also required. (See Part C of this guidance.)

FDA recognizes that condoms are used during anal intercourse for STD protection and would prefer that condoms be labeled for this use, provided appropriate testing is conducted. In order to modify the labeling, a clinical study of slippage and breakage during anal intercourse is necessary to assure that the properties of the new condom, such as physical attributes and device fit, as well as adverse effects are comparable when used this way. This study must provide sufficient detail and sample size to conduct a statistically valid comparative analysis of the study condom to a legally marketed condom. In summary, the material, design, and laboratory performance of the new male condom should be thoroughly studied prior to beginning any clinical studies. Results from the preclinical and clinical studies must demonstrate that the safety and effectiveness of the new condom is substantially equivalent to a legally marketed condom in order to proceed through the premarket notification process.

I. Feasibility (Safety) Testing

Prior to beginning slippage and breakage studies (see Section II below), the sponsor should conduct preliminary studies to evaluate the clinical performance (slippage and breakage) and acceptability of the condom. In addition, any episode of genital irritation with product use occurring in either the male or female should be promptly reported and the symptomatic individual should be carefully evaluated.

II. Slippage and Breakage Study

A. Objectives

Slippage and breakage studies evaluate the breakage, slippage and safety of the new condom for both partners in comparison to conventional latex condoms. Data concerning adverse events and acceptability should be collected.

B. Study Conduct

The new condom should be tested in actual use for slippage and

breakage in a randomized clinical study. Study subjects may be randomized to either the new condom or a legally marketed condom or may use both condoms in a randomized order. Breakage, slippage, partial slippage, and adverse event rates should be estimated and compared between the investigational condom and the legally marketed condom.

FDA recommends a randomized, cross-over study design for the slippage and breakage study. In general, at least 1000 uses of each type condom should be documented. A sufficient number of couples should be enrolled in the trial to ensure that each couple uses between three (3) and five (5) condoms of each type. However, these recommendations are general, and any clinical study must include justification for the proposed sample sizes (see section II. B. number 5 a-e).

The study subjects must be protected by using an effective, non-barrier means of contraception (e.g., hormonal contraception, intrauterine device (IUD), or male/female sterilization). An alternative would include a patient population at risk of pregnancy, but not planning pregnancy at the current time. However, if a condom breakage occurs during the study, these couples should either be willing to continue pregnancy or be willing to use emergency contraception. Please be advised that subjects may be considered at risk (as defined at 21 CFR 812.3(m)) under these circumstances. Please contact the FDA to discuss alternative study populations and applicable regulations.

The ideal study population would be at low risk of STDs. In geographic areas in which the gonorrhea and chlamydia prevalence is high, it is recommended that study participants be screened for these infections at study entry.

FDA recognizes that clinical trials may be conducted either as part of or outside of clinical care settings. Investigators should assure subject eligibility by history and, if concerns exist, by physical examination as well. Both men and women should be offered routine health care including a physical examination with screening and treatment for STDs. As many study participants may receive health care outside of the clinical trial, self-report of health care should be obtained. As women enter the study, Pap smear

screening should be offered or self-report of a recent, normal Pap smear should be obtained. Prior to study entry or during the study, if symptoms of STDs or concern about STDs exist, both partners should be screened and treated for STDs.

C. Study Design and Analysis

Provide detailed descriptions of the following elements of the protocol:

1. study hypothesis(es) to be tested;

2. study design and duration including randomization scheme and visit schedule;

3. participating study centers, their principal investigators;

Note: At least two centers should participate unless sufficient justification is provided. In addition, in order to comply with federal guidelines, minorities should be represented.

4. patient population; criteria for selection/exclusion of subjects:

a) sexually active, of reproductive age;
b) mutually monogamous;
c) willing and able to comply with study requirements;
d) protected from pregnancy by reliable, non-barrier method of contraception (see note below);
e) in good health as evidenced by history and/or physical examination (genital);
f) at low risk of sexually transmitted disease, including HIV infection and not having a medical history of recurrent, sexually transmitted disease;
g) agree not to use any vaginal lubricants or treatments except those products supplied by the study; and,

h) not allergic or sensitive to the study products.

Note: An alternative to selection criteria II.C.4.d. would include a patient population at risk of pregnancy, but not planning pregnancy at the current time. However, if a condom breakage occurs during the study, these couples should either be willing to continue pregnancy or be willing to use emergency contraception. Careful informed consent is essential. Please contact the FDA to discuss alternative study populations and applicable regulations.

5. sample size, including:

a) reference for formulas used to calculate sample size;
b) Type I error (à), Type II error ( );
c) expected breakage rate of the approved condom;
d) acceptable difference to be detected between the control and study condoms; and,
e) anticipated loss to follow-up rate.

6. data collection should include:

a) reproductive history;
b) demographic characteristics;
c) previous contraceptive experience including experience with condoms;
d) detailed reports of study condom use (including vaginal and anal use and all adverse events); and,
e) acceptability.

7. data collection instruments should include:

a) interview forms;
b) physical exam forms;
c) laboratory forms
d) coital logs; and,
e) detection and management of adverse events.

8. informed consent process and consent;

9. the protocol should specify all statistical procedures intended to compare the control and experimental condoms, provide and reference the formulas used to analyze the data and include:

a) description of the population (e.g., age, race, study site, reproductive history, previous contraceptive use, previous condom use, etc.); and, b) analysis by condom type with confidence intervals of the adverse events and the p-values for each statistical test, including: (1) description and rate for slippage (both partial and complete slippage); (2) description and rate for breakage; (3) description and rate of other adverse events, including, but not limited to genital mucosal irritation, bleeding and discomfort. (4) subgroup analysis of slippage/breakage/adverse events by: (a) age group; (b) race; (c) study site; (d) socioeconomic status; (e) educational level; (f) previous contraceptive use; and, (g) previous condom use. (5) reasons for study discontinuation by the subject; (6) total rate of study discontinuation and loss to follow-up; and, (7) test the hypothesis(es) stated above relating the results to the claim for the experimental condom.

10. Study and data monitoring procedures and quality assurance.

III. Contraceptive Effectiveness Study

A. Objectives

Contraceptive effectiveness studies evaluate the contraceptive effectiveness, safety, and ease of use of the study condoms compared to a legally marketed condom. Depending on the results of the Slippage and Breakage study, it may be necessary to "nest" a second Slippage and Breakage study within this efficacy trial.

B. Study Conduct

A randomized controlled clinical trial of at least six (6) completed menstrual cycles of product use should be done. See Introduction for a discussion of when an IDE application is needed. Study participation should include additional time to assure that the woman is not pregnant and no other adverse events have occurred during the study period.

In general, FDA recommends that approximately 400 study couples be enrolled in each investigational arm so that at least 300 study couples per arm complete the study. However, these recommendations are general, and any clinical study must include justification for the proposed sample sizes.

As stated in the introduction to this Part, the ideal study population would be at low risk of STDs. In geographic areas in which the gonorrhea and chlamydia prevalence is high, it is recommended that study participants be screened for these infections at study entry.

FDA recognizes that clinical trials may be conducted either as part of or outside of clinical care settings. Investigators should assure subject eligibility by history and, if concerns exist, by physical examination as well. Both men and women should be offered routine health care including a physical examination with screening and treatment for STDs. As many study participants may receive health care outside of the clinical trial, self-report of health care should be obtained. As women enter the study, Pap smear screening should be offered or self-report of a recent, normal Pap smear should be obtained. Prior to study entry or during the study, if symptoms of STDs or concern about STDs exist, both partners should be screened and treated for STDs.

C. Study Design and Analysis

Provide a detailed description of the following elements of the protocol:

1. study hypothesis(es) to be tested;

2. study design, entry and duration including randomization scheme and visit schedule;

3. participating study centers, their principal investigators;

Note: At least two centers should participate unless significant justification is provided. Each center shall contribute an

approximately equal number of study subjects in order to allow comparisons among investigators and sites.

In compliance with federal guidelines, minorities should be represented.

4. study subjects who are representative of the intended target population (e.g., age group, race, socioeconomic status, educational level, parity vs. nulliparity, etc.) for the marketing of the condom and include:

a) criteria for inclusion of subjects:

(1) sexually active (penile-vaginal intercourse, with a minimum of 6-8 coital episodes monthly);
(2) women age 18-40 and men age 18-50;
(3) mutually monogamous;
(4) willing and able to comply with study requirements including:
(a) men - able to understand instructions for condom use;
(b) women - willing to return to the clinic for pregnancy testing if indicated; and,
(c) couple - willing to use study condoms as sole method of contraception for study duration.
(5) in good health as evidenced by history and/or genital physical examination (Refer to paragraph in italics in Section III.B., above.);
(6) at low risk for sexually transmitted disease, including HIV infection and not having a medical history of recurrent sexually transmitted diseases;
(7) agree not to use any vaginal lubricants or treatments except those products supplied by the study;
(8) not allergic or sensitive to the study products;

(9) no known condition that might cause infertility;
(10) study subjects must be willing to accept the potential risk of pregnancy;
and,
(11) women with regular menses, including at least two normal cycles:
(a) after discontinuing hormonal contraception;
(b) postpartum or postabortion; or,
(c) after breast feeding.

b) criteria for exclusion of subjects:

(1) pregnancy, suspected pregnancy, or desire to become pregnant while
participating in the study;
(2) inability to participate in study for its duration or study subjects who are
unable to conform to the follow-up schedule;
(3) inability to remain sexually active for the study duration;
(4) multiple sexual partners;
(5) use of birth control methods other than the study condom;
(6) current or chronic infection of the reproductive tract;
(7) history of reproductive tract infection, surgery or condition that might
impair fertility;
(8) cervical cytology equivalent to Class III or worse;
(9) medical condition that would put the women at risk if she were to become
pregnant; and,
(10) allergy or sensitivity to the device.

Note: Study subjects who are currently using Depo-Provera (DMPA) or who have been prescribed and used DMPA within the last 9 months should be excluded from the study.

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 be excluded from the total number of study subjects required for analysis.

5. sample size including:

a) reference for formulas to calculate sample size;
b) type I error ( ), type II error ( );
c) expected pregnancy rate of the approved condom;
d) acceptable difference to be detected between the control and study condoms; and,
e) anticipated loss to follow-up rate.

6. data collection should include:

a) a complete medical history, including a detailed reproductive history, of both participants;
b) physical examination of both participants, when necessary (Refer to paragraph in italics in Section III.B., above.), to include:

(1) Female study participant;

(a) pelvic examination on entry and exit when applicable;
(b) Pap smears when applicable; and,
(c) Chlamydia and gonorrhea cultures when applicable:

(2) Male study participant

(a) genital examination on entry and exit when applicable; and,
(b) Chlamydia and gonorrhea cultures when applicable.

c) demographic characteristics;
d) previous contraceptive experience including experience with condoms;
e) detailed reports of study condom use (including

vaginal and anal use and all adverse events) and any other contraceptive use; and,

f) acceptability.

7. data collection instruments should include:

a) interview forms;
b) physical exam forms;
c) laboratory forms;
d) coital logs; and,
e) detection and management of adverse events.

8. informed consent process and consent.

D. Statistical Analysis

Statistical analyses of safety and effectiveness should be done via appropriate analytic models, to permit simultaneous statistical treatment of important outcome events. Analysis may be conducted at regular (specify) intervals to examine the data for trends such as specific adverse events. Appropriate actions should be taken if the periodic analysis so warrants.

1. statistical procedures should be referenced and justified and analyses should include:

a) description of the population (e.g., age, race, study site, reproductive history, previous contraceptive use, previous condom use, etc.);

b) analysis by condom type with confidence intervals for event rates and reporting of p-values for all statistical comparisons (analysis should include each site separately and also combined if pooling is justified) including:

(1) pregnancy rates;
(2) description and rate for breakage;
(3) description and rate for slippage (both partial and complete slippage);
(4) description and rate of adverse events, such as male and female genital tract

irritation or discomfort;

Note: Present the results with the p-values for each statistical test and place confidence bounds on each estimated adverse event rate.

(5) subgroup analysis of rates of pregnancy/condom breakage/condom slippage/adverse events by:

(a) age group;
(b) race;
(c) study site;
(d) socioeconomic status;
(e) educational level;
(f) previous contraceptive use;
(g) previous condom use; and,
(h) parity vs. nulliparity.

(6) description of reasons for and rate of study discontinuation include medical reasons, personal reasons, and dissatisfaction with the device, and loss to follow-up; and, (7) subject compliance.

Note: 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 reason). Both net and gross life table rates should be presented.

E. Data Reporting and Analysis

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.

The following specific data should be recorded and analyzed to evaluate safety and effectiveness of the investigational device compared to the legally marketed device:

1. date the pregnancy is discovered (Correlate to items #8 and/or #9 below); 2. date of infection, type, and method of diagnosis; 3. adverse events including, trauma to vagina, cervix, or penis; discomfort; pain; or any other reported adverse effects; 4. PAP smear reports and intake history (The same laboratory should be used for all PAP smears obtained during the investigation, where possible.); 5. device rupture, tear, or puncture; 6. slippage (both partial and complete) during use: how frequently and when; 7. subject compliance with device use; 8. subject use of emergency contraception; 9. level of acceptability - for study subject and partner; and, 10. device discontinuations, including: a. medical reasons (specify, e.g., allergy, infection, trauma, odor, itching, etc.); b. dissatisfaction with device (specify, e.g., inconvenient, uncomfortable, partner can feel it, subject can feel it, etc.); and, c. personal reasons unrelated to device (specify, e.g., desire to become pregnant, move from geographical area, etc.).

IV. Consumer Understanding of Labeling

Because the effectiveness of barrier contraceptive devices is so dependent upon proper use, contraceptive studies must also demonstrate how well the users will understand printed instructions for an over-the-counter (OTC) device.

During these studies, 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 consumers with limited education and/or literacy can understand printed instructions for an OTC device. Such studies should include well-constructed questionnaires, as well as clinical observations by health professionals to evaluate study subject understanding of the instructions.

As stated, FDA recommends that applicants conduct consumer field evaluations to determine a lay person's ability to properly use the device unassisted, by following the printed labeling instructions. Key features of such an evaluation are given below:

1. Lay users selected for the study should be of limited education and literacy. (Study subject selection criteria should be submitted to FDA with the study protocol and results.)

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

3. 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 study write-up should also contain the results of observations made by investigators.

PART C - INTERIM LABELING FOR A NEW MATERIAL CONDOM

INTERIM LABELING REQUIREMENTS FOR CONDOMS
MADE FROM NEW MATERIALS

I. Principal Display Panel

The principal display panel (21 CFR §801.60) must display the following:

"For Latex Sensitive Condom Users"

This is a [Blank] condom. This is not a latex condom. See Important Information on Back of Package.

II. Back Panel

The following Important Consumer Information must be placed on the back panel of the retail package, as well as within the package insert and with any promotional material:

Important Consumer Information: [Bold]

You may use this [Blank] condom if you or your partner are allergic to latex.

You should know:

The risks of pregnancy and sexually transmitted diseases (STDs), including AIDS (HIV infection), are not known for this condom. A study is being done.

There are laboratory tests on this [Blank] material. These tests show that organisms even as small as sperm and viruses like HIV cannot pass through it.

Latex condoms [Bold] for men, if used correctly with every act of vaginal intercourse, are highly effective at preventing pregnancy, as well as STDs, including AIDS (HIV infection).

CDRH/FDA: 10/25/94

ATTACHMENT A- INFORMATION FOR DETERMINING BARRIER PROPERTIES OF CONDOMS TO VIRUS PENETRATION

DIVISION OF LIFE SCIENCES
OFFICE OF SCIENCE AND TECHNOLOGY
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Introduction

This guideline addresses the rationale, methodology and required sensitivity of a test of the ability of condoms to act as barriers to transmission of the etiological agents of sexually-transmitted diseases (STDs), including viruses. The condom is identified in the code of

federal regulations (CFR) at Title 21 CFR Section 884.5300 as ..."a sheath which completely covers the penis with a closely fitting membrane. The condom is used for contraception and prophylactic purposes (preventing transmission of venereal disease)." The device may also be used to collect semen to aid in the diagnosis of infertility.

A medical claim for condoms as being effective against STDs requires that appropriate laboratory tests be performed. Since viruses are the smallest etiological STD agents and include the human immunodeficiency virus (HIV) and hepatitis B virus (HBV), the challenge particle should be a small virus or virus-size particle. Test conditions should account for as many parameters as possible that are considered to be important in real-life conditions. Appropriate choices of challenge particle, solution properties, and test pressure and duration are considered most important and must be included. The barrier properties of a condom may be determined in a static test, i.e., movement of the condom during the test is not required. Choices of parameters that make the in vitro test more stringent than expected real-life use are encouraged, with appropriate justification.

The choice of challenge particle has several important aspects. A biological assay may be preferred in general because there should be no "background" level of confounding "signal," as would be found with radioactively-or otherwise-labeled viruses or virus-like particles. Surrogate viruses of appropriate size and shape may substitute for human pathogens. Such surrogates may be bacterial viruses (bacteriophages), which are safer, faster and less expensive to use for testing and which can be readily obtained at sufficient titer to provide an adequate challenge concentration. However, in order for the test to be used to demonstrate safety with regard to STDs, the test virus should be smaller than hepatitis B virus (42 nm diameter), the smallest etiological agent for a STD. For these reasons, the following protocol suggests use of a small bacterial virus as challenge particle.

Preparation of Test Samples

Test condoms should be carefully handled so they are not damaged during the test procedure. Gloves may be worn as a precautionary measure to prevent abrasion or puncture by fingernails, rings, etc.

Most of accompanying lubricants and/or spermicides, if present, should

be removed so they don't interfere with the test. They may be removed by rinsing with buffer and gently patting dry.

The Basic Test

The test consists of filling the condom with virus-containing buffer and determining whether any viruses penetrate that barrier during submersion in collection buffer. Virus penetration is quantitated and reported as equivalent volume of challenge suspension needed to account for amount of virus penetration. The basic methodology using simple, readily-available equipment has been published (see Lytle et al reference). More sophisticated apparatus (see Retta et al reference) may be used to make the testing more convenient, although the basic test parameters should remain similar. The elements of the test should include:

1. attaching the test condom to an apparatus which:

i. provides a leakproof seal around the top and leaves an appropriate length of test portion available for the virus penetration test (at least 140 mm);

ii. provides for restraining of the condom to prevent overexpansion under pressure (Dimensions of the restrainer should allow expansion of the test portion of the condom to a length of 140-150 mm and a circumference of 120-130 mm. The contour of the restrainer should match that of the condom, including the reservoir tip, if present. Restrainers of the same size and material should be used with the test condoms and with the comparative condoms. In the case of a condom that is larger or smaller than a standard, an appropriate size restrainer should be used to accommodate the dimensions of the condom (must be justified).

iii. provides for exposure of the inside of the condom to aqueous challenge virus suspension;

iv. provides for application of pressure to that suspension;

v. allows for submersion of test portion of condom in collection fluid; and

vi. provides for access to challenge virus suspension inside condom for assay following the test.

2. filling the condom with a buffer that:

i. has appropriate properties (pH approximately 7.0, salinity of any one of several variations of physiological saline, surface tension less than 0.05 N/m [may be provided by 0.1% Triton X-100]) (Physiological saline has a lower viscosity than semen and therefore provides a more stringent test. The test may be performed at room temperature [68-72 F] when saline is used); and

ii. contains the challenge virus at sufficient titer, even at the end of the test (at least 108 plaque forming units/mL of a small, approximately spherical virus). The bacteriophage X174 may be used as the challenge virus. In the case of a virus other than X174, its use must be justified.

3. providing pressure to the challenge fluid equivalent to 60 mmHg (1.28 psi) or more (e.g., hydrostatically with a 810 mm column of water or with air/gas pressure);

4. providing a collection container with sufficient buffer to allow fluid contact with the test surface of the condom and to collect any virus that penetrates through the condom;

5. submerging the filled, pressurized condom (first 140 mm from the closed end, not including the reservoir tip, if present) in the collection buffer for at least 30 minutes;

6. assaying the collection buffer for the challenge virus to determine whether any virus has penetrated the condom and passed into the collection buffer (The collection fluid must be mixed at the time of assay so that the assay aliquots are representative.); and

7. calculating the equivalent volume of challenge virus penetration needed to account for amount of virus found in collection buffer.

Controls

It is known that some viruses can be removed from suspension by certain materials through binding, or that they can be rendered biologically

undetectable by chemical inactivation. Thus controls are needed to assure that the virus penetration test will yield meaningful data. Positive control experiments of the same duration are needed to assure that the overall test is functioning properly. Condoms with intentional pinholes may be used, although it is recognized that it is difficult to produce small pinholes.

In addition, it must be ascertained whether the challenge virus remains at a stable concentration in the condom during the test. Data from several condoms are needed and must be collected as part of each condom test. The titer of the challenge virus suspension inside the condom at the end of the test is compared to the titer originally placed in the condom. This determines if and how much the challenge virus titer changes during the test because of interaction with the condom and the test apparatus, or other factors.

It must also be ascertained whether any virus that penetrates the condom remains detectable in the collection buffer over the test period. This can be done by "spiking" the collection buffer with a low level of virus before a mock test (where there is no virus inside the condom and for the same duration) and assaying the titer of the collection buffer at the beginning and end of the mock test. This determines if and how much the penetrated virus titer changes during the test as a result of interaction with the outside of the condom, the restrainer or the collection container.

If either (or both) of the above controls indicates loss of virus titer, the starting challenge titer must be increased to compensate for the loss in order to maintain the overall sensitivity of the test.

It may be useful to determine via controls (e.g., settle plates) whether contamination caused by aerosolized virus or other leaks might lead to false evidence of virus penetration of the condom.

Sampling Procedure

A complete data set should include results from at least 60 condoms (20 condoms from each of 3 lots), in order to provide assurance that overall quality of each of three lots is satisfactory.

Comparative (predicate) samples

Latex condoms (off-the-shelf) are to be used. However, since the history (duration and temperature of storage) of such samples is not known and may affect the integrity of the samples, these samples must be used before the expiration date and should give virus transmission rates similar to those reported in the published literature. We suggest using non-lubricated, smooth (not ribbed, non-reservoir tip) samples. They should be treated in the identical manner as the investigational test samples, including mock removal of lubricant/spermicide, if appropriate.

Detection Limit

A typical method to determine the virus titer in the collection buffer would be to assay 1 mL in triplicate (3 mL total). In order to have 95% confidence that an assay will find at least one virus when virus is present [i.e., P(0) <0.05], the average number of infectious particles per total volume assayed must be at least three; e.g., there is a 95% probability that a titer of 1 pfu/mL will result in at least one plaque in a 3 mL total assay. Thus, the sensitivity or detection limit of this assay can be claimed as 1 pfu/mL when 3 mL is assayed. Detection limit expressed as volume of challenge virus suspension that penetrated the barrier is probably the most useful measure of test sensitivity. For example, in a real-life risk assessment the volume of transmitted virus-containing fluid can be translated into infectious units when the titer of a pathogenic virus (in real life) is known. The test procedure must be able to detect 2 x 10-6 mL penetration of the challenge virus suspension. This can be done by using a challenge titer of 1 x 108 pfu/mL, a collection buffer volume of 200 mL and assaying 1 mL in triplicate from the collection buffer (assuming no loss of virus titer in the challenge buffer nor in the collection buffer): the assay detection limit of 1 pfu/mL is equivalent to penetration by 200 pfu (1 pfu/mL x 200 mL) or 2 x 10-6 mL (200 pfu divided by 1 x 108 pfu/mL). Presentation of Results A table of the results for all the test condoms should be presented that includes: the challenge virus titer, the virus titer in the collection buffer, any correction factor for loss of virus (determined in the controls), and the calculated challenge volume that penetrated (for the condoms that allowed virus transmission). (See example below, Table I.) The volume of challenge virus suspension needed to account for the virus penetration into the collection buffer can be calculated for each condom by the method presented in the previous section. If some loss of virus titer occurs either inside the condom or outside in the collection container, the calculation should include the appropriate correction for such loss. For condoms that apparently did not allow virus transmission, the detection limit of that particular test should be given, e.g., as 2 x 10-6 mL. Report Forms Test results for virus penetration of

condom samples should be presented in tabular form, where the data for each condom are individually reported. Necessary items for each test sample are: i. date test was performed, ii. titer of challenge titer inside the condom at the end of the test, iii. calculated detection limit based on the challenge virus titer, the collection fluid volume, and the volume assayed, iv. pfu's found in aerosol control, v. pfu's detected in the collection fluid, vi. calculated titer of penetrated virus in collection fluid, and vii. volume of challenge virus suspension needed to account for the amount of virus detected in the collection fluid. Information accompanying the table should include: a. the challenge virus, b. the challenge and collection fluids (e.g., buffer and surfactant), c. how the titer of the challenge virus suspension was determined (dilution, volume assayed, and number of replicate assays), d. the challenge volume (if variable from one test sample to another, it should be included in the table for each condom), e. the collection fluid volume (if variable from one test sample to another, it should be included in the table for each condom), f. the transmembrane condom pressure and how it was provided (if variable from one test sample to another, it should be included in the table for each condom), and g. any evidence of an equipment or procedural malfunction during any particular test. Table I. Results for virus penetration through condom samples of Brand X, Lot #34068. i ii iii iv v vi vii Date Titer Detect Aerosol Collect Titer, Volume challenge limit control buffer collect penetra virus buffer virus (pfu/mL) (mL) (pfu) (pfu) (pfu/mL) (mL) 1 10/28 2.2x10^8 0.9x10-6 0,0,0 29,28,33 3.0x10^1 2.7x10-5 (+/-0.2) (+/-0.2) 2 10/28 2.3x10^8 0.9x10-6 0,0,0 0,0,0 <1 <0.9x10-6 (+/-0.2)

Positive Control

Reporting the results of the positive control experiment should be done using the same reporting format as with virus penetration of test samples.

Control to Test Challenge Virus Stability

Results from the test of challenge virus stability should be presented in tabular form, where the data for each condom are individually reported. (See example below, Table II.) Necessary items for each test sample are:

i. date test was performed,

ii. titer of challenge titer placed inside the condom at the beginning of the test,

iii. titer of challenge titer inside the condom at the end of the test, and

iv. calculated ratio of final to beginning titer.

Table II. Results of test for stability of challenge virus in condom samples of Brand X, Lot #34068.

Sample	Date	Beginning titer (pfu/mL)	Final titer (pfu/mL)	Ratio final/ begin
1	10/28/93	2.2x10^8 (+/-0.2)	2.1x10^8 (+/-0.2)	0.95
2				
3				

Control to Test Detection of Virus Which Penetrates Condom ("Spiking experiment")

Results from tests to determine the detection of penetrated virus should be in tabular form, where the data for each condom are individually reported. (See example below, Table II.) Necessary items for each test sample are:

i. date test was performed,

ii. virus titer in collection buffer at the beginning of the test,

iii. virus titer in collection buffer at the end of the test, and

iv. calculated ratio of final to beginning titer.

Table III. Results of test for detection of penetrated virus in contact with condom samples of Brand X,
Lot #34068.

Sample	Date	Beginning titer (pfu/mL)	Final titer (pfu/mL)	Ratio, final/ begin
1	10/28/93	1.2x10^2 (+/-0.1)	1.1x10^2 (+/-0.1)	0.92
2				
3				

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Retta, Herman, Rinaldi, Carey, Herman and Athey. Test method for evaluating the permeability of intact prophylactics to viral-size microspheres under simulated physiologic conditions. Sex. Trans. Diseases 18: 111-118,
1991.

More in Guidance Documents (Medical Devices and Radiation-Emitting Products) (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)

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