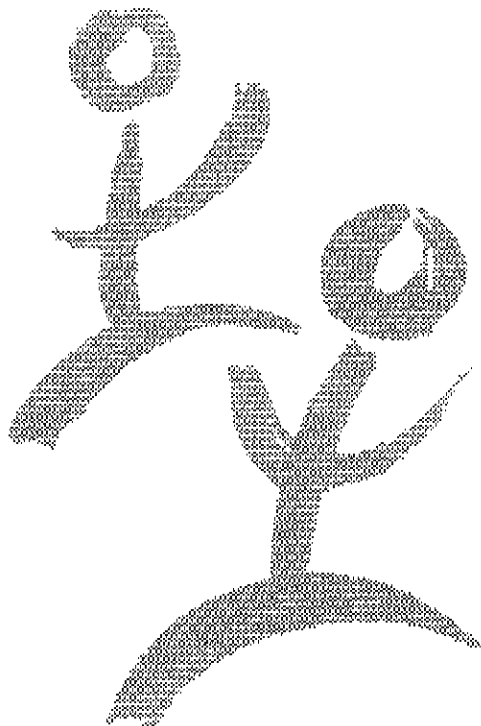




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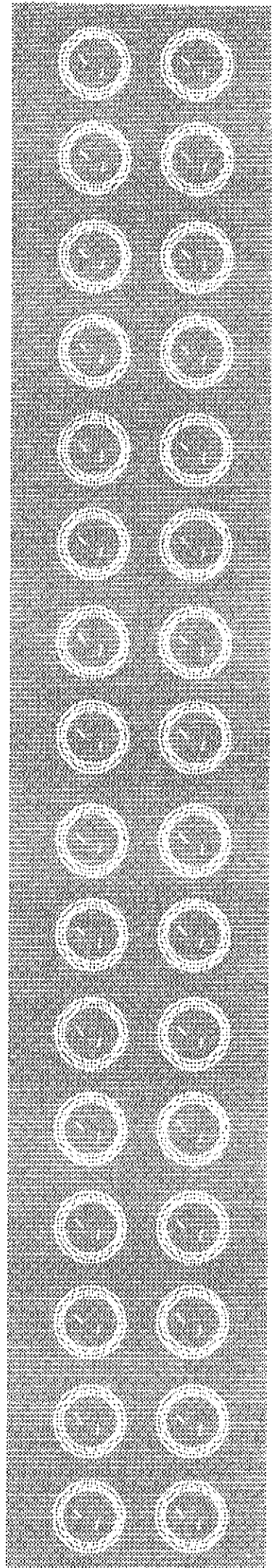
Preclinical and clinical requirements for approval to market non-latex condoms

Report and Recommendations of a
WHO Consultation on Preclinical and Clinical
Requirements for Non-Latex Male Condoms
Geneva, 13-15 May 1996



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Executive summary

There is an urgent need to develop new contraceptives that also protect against sexually transmitted disease (STD) and the human immunodeficiency virus (HIV), the cause of the acquired immune deficiency syndrome (AIDS). The UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, in collaboration with the Rockefeller Foundation and the Wellcome Trust, convened a consultation in Geneva, Switzerland, on 13–15 May 1996, which was attended by representatives of condom manufacturers, drug regulatory authorities and international condom experts to address the question of how to develop new non-latex male condoms.

The meeting had the objectives of: (1) reviewing the status of the development and marketing of non-latex male condoms including problems in research, manufacturing, licensing and registration; (2) discussing the similarities and differences in the current preclinical and clinical requirements for licensing and registration of latex male condoms and the non-latex female condom; and (3) making recommendations concerning preclinical and clinical regulatory and licensing requirements for the introduction of new non-latex male condoms into the marketplace.

The purposes of this report are to disseminate the conclusions of the consultation and to provide guidance to interested parties on how to obtain assurance on the safety and performance of new non-latex male condoms in a timely and cost-effective way. The report reflects the consensus achieved among the participants concerning the information that should be required for regulatory approval of non-latex condoms, and on the types of study needed to generate this information.

The following recommendations were made:

- Lengthy and expensive contraceptive efficacy trials are not needed to provide assurance that condoms made from new materials are as safe and effective as latex models. If the slippage and breakage rates of the new condoms are at least equivalent to those of conventional latex condoms, there is no reason to expect significantly different



rates of contraceptive efficacy.

- Impermeable non-latex condoms whose slippage and breakage rates are at least equivalent to those of conventional latex condoms that have been shown to meet international testing standards (e.g., ISO-4074), should have equivalent labelling as for latex condoms but additional substantiated claims may subsequently be allowed.
- Package labelling for condoms made of new materials as well as latex condoms should be more positive, and refer to their ability to protect against pregnancy and STDs.
- Protocols for premarketing studies in the future should be characterized by standardized definitions of the main parameters of breakage and slippage.

In addition to the recommendations above, the following conclusions were agreed to in the consultation:

- Manufacturers should screen new materials against commonly used vaginal lubricants and medication such as antifungal agents, mineral oil, petroleum jelly, spermicides, and alcohol-based products to assess possible interactions. Results should be reported in the proposed labelling.
- Some existing specifications for latex condoms are relevant to some new materials, but these specifications do not address all issues. Appropriate specifications can be developed for each new product based upon preclinical experience. However, it may

not be possible to develop one set of specifications for all types of non-latex condoms as each material is different. Each developer has the responsibility to defend the appropriateness of the parameters to his material.

- There is an assumption that products made from a new material will be for single use. However, the re-use of durable plastic materials is not uncommon, especially in developing country environments. While re-use is not recommended, given the realities in the field, research that will explore the efficacy of simple cleaning procedures and the durability of the component materials is needed.
- If the national regulatory authority requires minor modifications in the design of the product, this should not necessarily require a repetition of the slippage and breakage study.
- More research is needed in areas such as: (i) correlating laboratory tests with *in-vivo* use in order to understand better the clinical relevance of condom breakage; (ii) assessing slippage and breakage experience with anal intercourse; and (iii) developing proxy measures to test efficacy (such as detection of semen or prostatic secretion markers vaginally).
- Although biocompatibility and barrier properties to viral penetration will be established in the preclinical phase, these issues may need to be reassessed from time to time in order to control for problems that may arise with the product materials or with production.

Part I: Introduction, background and recommendations

INTRODUCTION

Until recently, consumers who wished to use a mechanical device to protect against unwanted pregnancy and/or sexually transmitted disease (STD) had only one choice: latex rubber male condoms. Although latex condoms come in a variety of colours, sizes and styles, they are all made from natural rubber. The appearance of the first plastic male condom¹ on the USA market in 1994 marked the beginning of an era where barrier products made from synthetic materials will be developed and marketed.

Currently, in addition to the above-mentioned polyurethane product, there are several other non-latex male condoms that have obtained initial marketing clearance from the Obstetrics-Gynecology Devices Branch of the United States Food and Drug Administration (FDA) or are awaiting such clearance. In theory, this new generation of plastic male condoms offers the consumer a number of potential advantages, including greater sensitivity, greater strength, a longer shelf life, freedom from allergic reactions, and compatibility with a wider range of lubricants. This should be welcome news to consumers and encourage health care professionals who believe that an expanded choice of products will lead to wider usage.

Non-latex condoms have different physical, stability and toxicological characteristics than latex condoms. In the USA, for example, developers must submit detailed information on these characteristics and on clinical breakage²/slippage³ characteristics to

the FDA for clearance prior to marketing. Because the materials from which the non-latex male condoms are made are new for this use, the FDA requires a full range of preclinical data on the material, its manufacturing process and its safety before the start of clinical studies. The FDA also requires data on contraceptive efficacy compared with that of a latex condom in order to permit marketing of the product with unrestricted labelling.

Without such data, the FDA requires that non-latex condom must carry labelling that states the product is for use by "latex-sensitive condom users".

In view of the public health interest in increasing condom use, it is recognized that successful private sector involvement in the development of innovative products is vital. Better products can improve acceptability, which in turn is likely to increase use. The commercial sector can bring new products to market and encourage increased and correct use.

The development of a new condom is expensive. In addition to the costs of research and development, there are considerable outlays for mass production equipment, quality control systems, product development and marketing. The actual costs and time needed to complete the full range of preclinical and clinical studies are not precisely known and may vary depending upon a number of factors including the type of material under evaluation. However, it is known that work on some of the non-latex condoms began almost a decade ago and that the costs run into many millions of US dollars. The time and effort required to obtain

A male condom is defined as a sheath made of an impermeable barrier material that is designed to cover the penis and which will prevent the exchange of body fluids during sexual intercourse. The position of the World Health Organization is that when used correctly and consistently, male condoms of good quality are a highly effective means of protecting users and their partners against unplanned pregnancy as well as sexually transmitted diseases.

¹For the purposes of this report the terms "plastic condoms" and "non-latex condoms" are synonymous and do not refer to "skins" or condoms derived from sheep's caecum. The female condom made of polyurethane (Femidom™ or Reality™) is a product designed to be used by women and is not addressed in this report.

²By "slippage" is meant the condom slipping off the erect penis prior to penile withdrawal at the completion of intercourse.

³By "breakage" is meant the development of splits, tears, or holes in the condom during use.

regulatory clearance and approval, and the associated costs, are of paramount importance to developers who wish to bring their new products to the market as quickly as possible. Clearly, the cost of bringing a new product to market has a major influence on the pace of development, the eventual scope and number of product innovations that can be pursued and, very importantly, on the final price of the product to the consumer.

It is known that the costs incurred by developers of new products are time-dependent. The conduct of various clinical studies and the review and approval process can be time-consuming. A comparative multicentre contraceptive efficacy trial, for example, will take at least 18 months to complete and can cost, per condom type, more than \$2 million.

In the USA, where most of the experience is being gained in the development of regulatory approaches to marketing approval for new male condoms, there is a special route, the 510(k) or Premarket Notification process, for new products that claim substantial equivalence to existing latex condoms. At the present time, this approach requires the conduct of comparative clinical slippage and breakage studies prior to marketing clearance. Such studies are typically conducted in a population at low risk of pregnancy with couples using an effective non-barrier form of contraception. This makes it possible for registration under abbreviated investigation device exemption (IDE) regulations, which involve less paperwork than a full IDE. The FDA permits developers, following successful completion of

preclinical performance and clinical slippage and breakage studies, to market their new products while simultaneously conducting a comparative contraceptive efficacy trial. However, during this post-marketing period before the results of the efficacy trial are available, the developer is required to use interim labelling that indicates usage of the new product should be only by persons with latex sensitivity.

Stringent regulatory requirements may inhibit the development of devices with radical changes in design and/or material. In practice, as major innovations require more elaborate regulatory approval procedures, new products may be less innovative in order to reach the market more cheaply and quickly. As a consequence, it may be necessary to encourage innovation by developing more risk-sharing approaches between public- and private-sector agencies. In this era of STD/AIDS and rising teenage pregnancy rates, consideration must be given to how the government's responsibility to protect public health can best be balanced with the consumers' right to access new products.

The deliberations of the consultation were particularly facilitated by the availability of two documents: "*Testing guidance for male condoms made from new material*" prepared by the FDA (1) which served as a basis for discussion in the consultation; and a paper by Steiner et al. (1994) entitled "*Standardized protocols for condom breakage and slippage trials: a proposal*" (2).

BACKGROUND

Once considered an ineffective contraceptive method of dubious lineage, the status of the male condom has risen in proportion to the growing awareness of STDs, especially HIV/AIDS, as a public health problem. At the same time that family planning programme managers were beginning to see the advantage of involving male partners in contraception, social marketing programmes, which needed products that did not require a doctor's prescription to sell over the counter, began to promote condoms as a family planning method and prophylactic against STDs, which emphasized male responsibility. As pharmaceutical firms continue to operate in an increasingly negative environment for the development of new hormonal contraceptives, male condoms, which protect against many STDs as well as pregnancy, are becoming even more attractive to programme managers. In the world of marketing, competition can be healthy and the addition of other products tends to stimulate overall demand. Consumers, family planning clients included, respond favourably to having a greater range of choice.

Latex male condoms have a number of advantages that are peculiar to their material and design: used correctly and consistently by a conscientious user, they provide good contraceptive and STD protection and have no systemic effects. Available in small packages, they can be discreetly carried or stored. They are affordable and easy to use. In most cases, "one size fits all" eliminating the need for an array of sizes. They have been on the market for more than half a century and are widely known and well accepted. With improvements in manufacturing technique and quality control, it is possible to be confident that the product, when used properly, will perform as expected.

Disadvantages of latex male condoms fall into two general categories: those that discourage users and those that influence programme managers. Consumers complain about interruption of the sex act, loss of penile sensation, odour, taste, etc. Some people—a small percentage of users—are sensitive to latex and risk an allergic reaction if they use a latex product. Programme managers would like a product

that is effective, easy-to-use and less vulnerable to the vagaries of consumer mishandling, such as the use of oil-based lubricants that damage latex condoms. There is concern about the stability of biodegradable latex products during storage. Because latex rubber is easily weakened if exposed to light, air, ozone and humidity, especially over long periods of time, properly sealed, impermeable packaging is now required by all national and international standards authorities. This concern about shelf life is important in many, especially developing, countries.

During World War II, when latex rubber was scarce, nylon condoms are said to have been on the market briefly in the USA. In the late 1960s, the Population Council started work on the development of a plastic condom that was intended to be stronger and have a longer shelf-life than latex models. Work on the early prototypes stopped when problems arose with the candidate materials.

By the late 1980s, interest in the potential of non-latex condoms emerged in several quarters. In 1996, there were at least six firms and agencies involved in the development of plastic condoms. All have, or will have, marketing operations in the USA. The firms include: London International Group, Tactyl Technologies Inc., Ansell Inc., Carter-Wallace Inc., Sagami Rubber Industries Co. Ltd. and Mayer Laboratories Inc. Other partners in development include: the US National Institutes of Health (NIH); the Contraceptive Research and Development (CONRAD) Program, a non-governmental agency based in Norfolk, VA, USA; Family Health International, a nongovernmental agency based in Research Triangle Park, NC, USA; Health Decisions, Inc., a research company in Chapel Hill, NC, USA; and WHO.

Today's barrier products must not only be resistant to breakage and free from holes, but they must also be impermeable to microbial and viral penetration. Efficacy as a barrier to sperm and infectious agents such as HIV is essential. Pinholes resulting from the dipping process used in manufacture can occur in latex rubber and inter-factory variations in the latex formulation and production process can, on occasion, lead to the appearance of nonhomogeneous products in the market.

The main new materials under consideration for condoms are thermoplastic elastomers including polyurethanes. Non-latex products have design characteristics that should give them an advantage over latex. The materials from which current models are made are believed to be stronger, thinner on average (and, thus, theoretically more sensitive), more homogeneous, less biodegradable, odourless, tasteless, hypoallergenic and impermeable to the smallest viruses. Some non-latex materials can be used with oil-based lubricants and spermicides. Most non-latex models rely upon material tensile strength to provide the needed resistance to breakage; in contrast, the ability of a latex condom to resist breakage is believed to be associated with the elasticity of the material. In both cases, material lubricity is also believed to be a factor.

For the foreseeable future, there will not be more than a limited number of non-latex brands on the market. Each of the new models currently under development is a protected, proprietary venture. Each is subject to rigorous pre-market scrutiny by the FDA. It is unlikely, therefore, that non-latex condoms will be affected by the same quality fluctuations that characterise the present-day global production of latex condoms which are supplied by more than fifty different factories worldwide working to differing standards of quality.

It now seems unlikely that the hope of developing a plastic condom technology that would permit simple, inexpensive local manufacture and distribution in developing countries, will be realized, at least in the near future. The cost and complexity of manufacture argue against establishing plants in developing countries until sales in industrialized countries can generate sufficient revenue to cover development costs. Market-driven licensing arrangements between the developers and commercial companies in some developing countries are possible, but these agreements may price the products beyond the reach of poorer consumers.

Public sector pricing agreements, such as the one between WHO and Tactyl Technologies Inc. and between Family Health International and its commercial partner, Mayer Laboratories Inc., could succeed in making low-cost non-latex products accessible to developing country programmes.

For the time being, then, the main disadvantage of non-latex condoms is likely to be their cost. Changing from natural rubber latex-dipping technology to non-latex solvent-based or extrusion/film-based manufacturing processes is a major technical, production and marketing innovation with significant financial implications, and many uncertainties.



RECOMMENDATIONS AND CONCLUSIONS

The main objective of the participants in the three-day consultation was to make recommendations concerning preclinical and clinical regulatory and licensing requirements for non-latex male condoms. As a result of the consultative process, the participating developers, manufacturers, regulators and researchers achieved consensus on (1) the type of data needed to obtain regulatory approval for condoms made from new materials, and (2) the types of study required to generate this information. The consultation prepared the following recommendations and conclusions which are listed below as well as being incorporated into Part B of this report.

Recommendations

1. Lengthy and expensive contraceptive efficacy trials are not needed to provide assurance that condoms made from new materials are as safe and effective as latex models. If the slippage and breakage rates of the new condoms are at least equivalent to those of conventional latex condoms, there is no reason to expect significantly different rates of contraceptive efficacy.
2. Impermeable non-latex condoms whose slippage and breakage rates are at least equivalent to those of conventional latex condoms that have been shown to meet international testing standards (e.g., ISO-4074), should have equivalent labelling as for latex condoms but additional substantiated claims may subsequently be allowed.
3. Package labelling for condoms made of new materials as well as latex condoms should be more positive, and refer to their ability to protect against pregnancy and STDs. (For an example, see box on page eight of this report).
4. Protocols for premarketing studies in the future should be characterized by standardized definitions of the main parameters of breakage and slippage.

Conclusions

In addition to the recommendations above, the following conclusions were agreed to in the consultation:

1. Manufacturers should screen new materials against commonly used vaginal lubricants and medication such as antifungal agents, mineral oil, petroleum jelly, spermicides, and alcohol-based products to assess possible interactions. Results should be reported in the proposed labelling.
2. Some existing specifications for latex condoms are relevant to some new materials, but these specifications do not address all issues. Appropriate specifications can be developed for each new product based upon preclinical experience. However, it may not be possible to develop one set of specifications for all types of non-latex condoms as each material is different. Each developer has the responsibility to defend the appropriateness of the parameters to his material.
3. There is an assumption that products made from a new material will be for single use. However, the re-use of durable plastic materials is not uncommon, especially in developing country environments. While re-use is not recommended, given the realities in the field, research that will explore the efficacy of simple cleaning procedures and the durability of the component materials is needed.
4. If the national regulatory authority requires minor modifications in the design of the product, this should not necessarily require a repetition of the slippage and breakage study.
5. More research is needed in areas such as: (i) correlating laboratory tests with *in-vivo* use in order to understand better the clinical relevance of condom breakage; (ii) assessing slippage and breakage experience with anal intercourse; and (iii) developing proxy measures to test efficacy (such as detection of semen or prostatic secretion markers vaginally).
6. Although biocompatibility and barrier properties to viral penetration will be established in the preclinical phase, these issues may need to be reassessed from time to time in order to control for problems that may arise with the product materials or with production.

It is hoped that the recommendations in this report will be useful to regulatory authorities in developing and industrialized countries when approval is sought to introduce and to market non-latex male condoms.

Part II: Recommended preclinical and clinical protocols for the testing of male condoms made from new materials¹

The following guidelines were adopted to reflect the group's consensus on the pre-clinical and clinical testing requirements for any male condom made from new material.

PRECLINICAL REQUIREMENTS

The following information, to be developed by means of preclinical investigations, should be made available to demonstrate that the candidate product, including all of its materials and processes, is safe for human use. This list of requirements will not be inclusive or specific for all non-latex materials.

A. General information

1. Identify a control device for comparison with the study device in terms of intended use, design, materials, specifications, and performance.
2. Provide copies of labels, labelling, and advertisements sufficient to describe the new device, its intended uses and directions for its 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, including:

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 specification of 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).
8. The lubricant(s) formulation, chemical composition of each ingredient, ingredient specifications, and quantity of lubricant applied to 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. For a solvent-based manufacturing process (blown, spun or dipped), details of:
 - a. solvent(s);
 - b. compounding additives including any colour additive that may be added (if a colour additive is used, provide its chemical composition and identify its colour index number and reference the specific colour additive listing—see reference 5);
 - 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. For an extrusion/film-based manufacturing process (with seam welds), provide details of:
 - a. data from physical testing conducted on the extrusion/film material using appropriate sampling procedures (see section E.2.);

¹See references 1, 2, 3, and 4.



- b. data on the quantities of residual solvent(s) and additives in the film;
- c. compounding additives that may be included (6) (if a colour additive is used, provide its chemical composition and identify its colour index number and reference the specific colour additive listing—see reference 5);
- 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).

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

D. Material toxicity

The following material toxicology information should be provided:

1. A summary of known toxicity data on all the monomers, additives, solvents used in the manufacturing of the material(s) of the condom.

2. Toxicity data on dusting agents and lubricants.

3. Using ISO-10993 (6), and consistent with a "surface device" and repeated contact with mucosa and possibly compromised tissue surfaces,

biocompatibility data on finished (packaged, ready for distribution) product demonstrating that the condom material does not produce toxicity, including cytotoxicity, sensitization (polar and non-polar), mucosal irritation, acute systemic toxicity and subcutaneous implantation (90 day) test.¹ (If there is evidence of systemic absorption of any components and residuals, mutagenicity testing should be performed.)

E. Finished product

The following information on the finished condom should be given:

1. A complete description of the 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 physical testing conducted on the finished condom using appropriate sampling procedures and established performance limits and tolerances (cross reference with section F).

3. The following list of physical properties should be reviewed to determine the relevance of each as a means to assess any new material device:

a. tensile strength (although the material may need to be assessed biaxially);

b. energy/toughness (assess the area under the stress-strain curve);

c. force at break;

d. elongation;

e. tear resistance and propagation;

f. tensile set/creep (hysteresis at different maximum strains to assess return to permanent set);

g. fatigue at 100% extension;

h. coefficient of friction test;

i. water leakage test (considering whether the material may be hydrophilic);

¹The ISO standard identifies the implantation test for this kind of product as only required on a case-by-case basis. The participants in the consultation agreed that supporting data may include results obtained from non-animal models as appropriate.

- j. air inflation, volume and pressure (burst may be replaced by cyclic test); and
- k. special tests to assess elasticity/efficacy of retention mechanism design.

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

F. Quality control/quality assurance

1. Provide detailed description of test procedures to establish the quality of each condom lot or batch (cross reference response with the flow diagram, section C.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 description of the 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, the applicable sampling plan and inspection level for each test (provide also 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 data to demonstrate the reproducibility and sensitivity of the test and the specifications and operating procedures, and calibration procedures.

3. Information on the air inflation test to include a detailed description of how the test is conducted including data to demonstrate the reproducibility

and sensitivity of the test and the 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 viral penetration data from *in-vitro* comparative studies simulating actual use conditions to demonstrate the barrier properties, i.e., impermeability of the test condom with respect to STD organisms (1). Bacteriophage x-174 is recommended as the surrogate marker in the viral penetration study. The latex control condom should be one that is currently marketed in the country where the study is being conducted.

I. Shelf life

Real-time and/or accelerated data is used to substantiate the claimed shelf life. Testing should include, but not be limited to, evaluation of the condom and lubricant system after storage in the primary packaging system for materials compatibility and spermicidal effectiveness (if applicable). Testing for shelf life should 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);
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 Agree Test for Total Spermicidal Power) (7).

CLINICAL REQUIREMENTS

Once all preclinical steps are completed and the necessary preliminary data have been obtained that demonstrate the safety of the experimental condom, it is possible to begin clinical studies.

A. Feasibility (safety) testing

Before embarking on full clinical testing, a small-scale preliminary clinical safety study in a population at low risk of pregnancy should be conducted to evaluate the slippage and breakage performance of the test condom and its acceptability, including evaluation of any evidence of immediate adverse effects such as genital irritation. Upon satisfactory completion, a full-scale slippage and breakage study should be initiated to evaluate safety and performance of the new condom in comparison with latex condoms.¹

B. Slippage and breakage study

Slippage and breakage studies evaluate the slippage, breakage and safety of the new condom for both partners in comparison to a currently marketed conventional latex condom that meets international testing standards. Data concerning adverse events and acceptability should be collected.

Slippage and breakage are relatively uncommon events. A review of the condom literature suggests that condom breakage rates range between <1% to 12%; many of the studies conducted in recent years indicate rates for both events in the 2-5% range. Given the possibility of variation, it would be desirable, when designing a full-scale slippage and breakage study, to ensure that there is sufficient study detail and a large enough sample size for a statistically valid comparison between the new condom and a marketed latex condom.¹

¹Currently, the latex rubber condom is the *de facto* "gold standard" against which new products are compared. Once condoms made from new materials are available on the market, it is possible that one of them would become an appropriate "nearest equivalent" condom for future comparative studies.

Much of the variation in slippage and breakage study results can be traced to inadequacies in study design. As noted by Steiner *et al.* (2), studies report considerable variation in rates of breakage and slippage, "in part, because these events have been defined differently and the instruments used to collect data vary widely across the studies".

Clear distinctions among these parameters are recommended, specifically:

- *Non-clinical breakage rate.* The number of condoms reported to have broken while the package was being opened or while the condom was being donned divided by the number attempted to be used in the study.
- *Clinical breakage rate.* The number of condoms reported to have broken during intercourse or withdrawal divided by the number of condoms used during intercourse during the study.
- *Total breakage rate.* The sum of the number of condoms reported to have broken divided by the number of condoms attempted to be used in the study.
- *Complete slippage rate.* The number of condoms reported to have completely slipped off the penis during intercourse or withdrawal divided by the number of condoms used during intercourse during the study.
- *Total clinical failure rate.* The number of condoms reported to have broken during intercourse/withdrawal or slipped off completely divided by the number used during intercourse during the study.
- *Total failure rate.* The number of condoms that have broken (both non-clinical and clinical) or slipped off completely divided by the number attempted to be used in the study.

A randomized cross-over study design of at least 1000 uses of the control and at least 1000 users of the test condoms where each couple uses at least 3-5 condoms of each type is recommended. For example, the study design could address 200 couples using five condoms of each of the two types in at least two study

sites. However, these recommendations are general and any clinical study must include justification for the proposed sample sizes (see section C 7, *a-e*, below).

The study subjects must be protected from pregnancy by using an effective, non-barrier means of contraception (e.g., hormonal contraception, intrauterine device, 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 condom breakage occurs during the study, the affected couples should either be willing to continue pregnancy or be willing to use emergency contraception. The ideal study population would be the one that is at low risk of STD. In geographical areas in which gonorrhoea and chlamydia prevalence is high, it is recommended that study participants be screened for these infections before entering the study.

It is recognized 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 STD. As many study participants may receive health care outside of the clinical trial, self-reports of health care received should be obtained. As women enter the study, cervical cytological screening should be offered or evidence of a recent, normal cytology should be obtained. Prior to study entry or during the study, if symptoms of STD or concern about STD exist, both partners should be screened and treated for the STD.

C. Study design and analysis

Detailed descriptions of the following elements of the protocol should be given:

1. Study hypothesis(es) to be tested.
2. Study design and duration including randomization scheme and visit schedule.

3. Participating centres and the principal investigator(s).

4. Selection of appropriate latex condom control for blind, or double-blind where possible, comparison. (The latex control condom should meet current ISO standards and should currently be marketed in the country where the study is being conducted.)

5. Laboratory quality tests to characterize the study products to control for factors such as lubricant quantity, viscosity and size and to facilitate comparisons between them.

6. Study population (including criteria for selection/exclusion of subject; where they exist, minorities should not be excluded):

- a.* sexually-active, of reproductive age;
- b.* mutually monogamous couples;
- c.* willing and able to comply with study requirements;
- d.* protected from pregnancy by a reliable, non-barrier method of contraception;¹
- e.* in good health as evidenced by history and/or physical examination (genital);
- f.* at low risk of STDs including HIV infection, and not having a history of recurrent STDs;
- g.* agreeing 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.

7. Sample size, including:

- a.* reference for formulae used to calculate sample size;
- b.* type I error (α) and II error (β);
- 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.

¹An alternative to this selection criterion would include a patient population at risk of pregnancy but not planning pregnancy at the current time. However, if condom breakage occurs during the study, the affected couples should either be willing to continue pregnancy or to use emergency contraception. It is essential to obtain informed consent carefully.



8. Data collection should include the following and should recognize and take into consideration possible effects of couples who break condoms more frequently than expected, levels of user experience, and pregnancy risk status:

- a. reproductive history;
- b. demographic characteristics;
- c. previous contraceptive experience including experience with condoms;
- d. detailed reports of study condom use including slippage and breakage, as described in Table 2, and vaginal and anal use and all adverse events; and
- e. overall acceptability.

9. Data collection instruments should include:

- a. interview forms;
- b. physical examination forms;
- c. laboratory forms;
- d. coital logs; and
- e. adverse events forms.

10. Informed consent process and consent.

11. The protocol should specify all statistical procedures intended to compare the control and

experimental condoms, provide and reference the formulae used to analyse the data and include:

- a. description of the population (e.g., age, race (where applicable), 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:
 - i. description and rate for complete slippage;
 - ii. description and rate for breakage;
 - iii. description and rate of other adverse events, including, but not limited to genital mucosal irritation, bleeding and discomfort;
 - iv. subgroup analysis of slippage/breakage/adverse events by:
 - age group
 - race (where applicable)
 - study site
 - socioeconomic status
 - educational level
 - previous contraceptive use
 - previous condom use;
 - v. reasons for discontinuation by the subject;
 - vi. total rate of study discontinuation and loss to follow-up; and

Table 1. Number of condom uses required per study group to demonstrate equivalence (80% power, 95% level, 1-sided test)

Clinical breakage or complete slippage rate	Minimal difference between groups		
	1%	2%	3%
1%	1,225	307	137
2%	2,424	606	270
3%	3,599	900	400
4%	4,749	1,188	528
5%	5,874	1,469	653
6%	6,974	1,744	775
7%	8,050	2,013	895
8%	9,101	2,276	1,012
9%	10,128	2,532	1,126
10%	11,129	2,783	1,237

vii. test the study hypothesis(es) stated above relating the results to the claim for the experimental condom.

While adverse events such as pregnancy or STD infection need to be included in the report of the study, they are not to be used for calculation of pregnancy or STD rates.

12. Study and data monitoring procedures and quality assurance.

13. The mechanical properties of the manufactured lots used in the clinical studies (both latex and non-latex) should be fully characterized before and, where necessary, at the end of the study.

Although the consultation did not recommend that a contraceptive efficacy study should be conducted in all cases, the participants concluded that it would be useful to employ post-marketing surveillance, a technique commonly used to monitor more extensive in-use experience, to monitor and assess unplanned pregnancy, genital irritation and any other adverse events.

Table 2: Types of information to be collected in trials of condom breakage and slippage¹

Breakage— <i>when</i> condom broke	<ul style="list-style-type: none"> • while removing from package • during intercourse • during withdrawal • while removing condom from penis
Breakage— <i>where</i> condom broke (provide diagram)	<ul style="list-style-type: none"> • rim • shaft • tip
Slippage (complete and incomplete)	<ul style="list-style-type: none"> • slipped down but not completely off the penis (how far down?) • during intercourse • during withdrawal (was condom rim held against base of penis?) • slipped completely off the penis during intercourse • slipped completely off the penis during withdrawal (was condom rim held against base of penis?)
Partner type	<ul style="list-style-type: none"> • monogamous (exclusive) relationship • primary partner
Lubricant	<ul style="list-style-type: none"> • type and amount of additional lubricant used
Type of intercourse	<ul style="list-style-type: none"> • vaginal • anal • oral

¹Modified from reference 2.



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The UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) is the major research arm of the World Health Organization's reproductive health programme, which functions as a partnership between HRP, the WHO Division of Reproductive Health (Technical Support), and relevant parts of the WHO Units of Women's Health and Adolescent Health and Development.

HRP brings together administrators, policy-makers, scientists, clinicians and the community to identify and address research priorities aimed at improving reproductive health throughout the world. Cosponsored by the United Nations Development Programme, the United Nations Population Fund, the World Health Organization, and the World Bank, HRP is also the main research programme of the United Nations system for research in reproductive health.

HRP investigates the extent and nature of reproductive health problems and the influence of behaviours and quality of services. It gathers information on the needs and perspectives of women and men in developing countries. Governments need this information for developing sound policies for the provision of reproductive health services.

HRP also conducts research to improve reproductive health technologies. It helps developing countries to meet their own research needs and to participate in global reproductive health research. HRP's work contributes to the development of norms, standards and guidelines in reproductive health research, services and ethics.

HRP's current research priorities include:

- development of new methods of fertility regulation for both women and men;
- the introduction of methods into family planning programmes;
- study of the long-term safety of contraceptive methods already in use and other aspects of epidemiological research in reproductive health;
- study of social and behavioural aspects of reproductive health;
- development of methods for controlling the spread of sexually transmitted disease which can cause infertility.

