



Female Condom Technical Review Committee

Background

The female condom offers women an alternative method of STI/HIV and pregnancy prevention when male condoms are not or cannot be used. Research has shown that the Reality® female condom, which is manufactured by the Female Health Company, is comparable to other barrier methods in its effectiveness in preventing pregnancy and STIs. Since the mid 1990s, the product has been distributed in the public sector as part of HIV/AIDS reduction programmes where it provides an important alternative to the male condom. However, because of its high cost compared to latex male condoms (approximately 20 times for public sector distribution) the female condom has achieved only limited distribution in countries hardest hit by the HIV/AIDS epidemic. Recently, the Female Health Company has developed a second generation product made from synthetic latex and new designs of female condom have been developed by other companies. These newer designs offer the prospect of lower manufacturing costs and therefore are of immediate interest to public sector agencies.

Currently, there is no international standard for female condoms (International Standards Organization Technical Committee ISO/TC 157 is developing a standard but it is unlikely to be published for at least another two years), so the effectiveness and safety of each design has to be evaluated by experts on an individual basis. Given this situation, the United Nations Population Fund (UNFPA) requested the World Health Organization, Department of Reproductive Health and Research (WHO/RHR), to review the second-generation synthetic latex female condom (FC2) produced by the Female Health Company as well as the Reddy Latex Female Condom manufactured by Medtech Products Limited, and provide guidance on whether these products can be included in the UNFPA public-sector procurement programmes. In addition, WHO/RHR, in collaboration with UNFPA, agreed to evaluate dossiers provided by other manufacturers of both latex and synthetic female condoms that are either under development or are due to come onto the market in the near future. The Family Health Company Ltd.,

United Kingdom, Medtech Products Ltd., India, and Natural Sensation Compania Ltda, Colombia, were requested to submit dossiers for review.

The Review Process

A team of internationally recognized technical experts and advisors, the *Female Condom Technical Review Committee* was established by WHO/RHR in January 2006, to conduct the review. The technical experts (see Annex 1A) were experienced in condom research, design, manufacture and testing as well as public-sector procurement, the regulation of female condoms and conducting clinical trials on condoms. Technical advisers (see Annex 1B) selected from collaborating agencies, research institutes, national and international standards organisations and regulatory bodies with particular interest in male and female condom development, regulation and marketing, also participated in the review process.

The objectives of the review are summarized below:

- To agree a set of criteria for reviewing female condom products.
- To review and develop a consensus definition of clinically significant failure modes for female condoms.
- To review the dossiers provided by the manufacturers to assess the safety of the materials and lubricants used and product design, including chemical and physical specifications, and assess data to support shelf-life, packaging and storage requirements.
- To review the manufacturing process and quality-assurance issues including procedures, test methods, requirements, sampling, audits, and regulatory and quality systems approvals/certification.
- To review the available clinical information to determine the safety, effectiveness and performance of the product and its acceptability.

The team of technical experts of the *Female Condom Technical Review Committee* met on 16 January 2006 to review the evidence on female condom failure modes, draft the



definition of female condom failure modes, and prepare draft criteria for assessing products under review. The technical advisers of the *Female Condom Technical Review Committee* then joined the technical experts on 17 and 18 January 2006. The full Committee first reviewed and reached consensus on the definitions of female condom failure modes (see Annex 2). The draft criteria for assessing products were then presented for discussion, modification and endorsement by the technical advisers.

After consensus was reached on the assessment criteria, participants were divided into two subgroups, one to consider design and clinical issues and the other to consider technical issues including materials, manufacturing process and quality assurance. Each sub-group reviewed the manufacturers' dossiers in accordance with the agreed criteria and presented their conclusions during a plenary session.

The team of technical experts of the Committee drafted recommendations and separate confidential reports for each manufacturer. The recommendations and reports were presented to all Committee members for discussion and endorsement. The confidential reports on the outcome of each review were then submitted to the respective manufacturers. These reports initiated an ongoing review process, in which additional information requested from the manufacturers is then reviewed by the technical experts. If necessary, further information was sought until all issues raised had, in the opinion of the technical experts of the Committee, been adequately addressed. Final recommendations on each product were then made.

Review Criteria

The following criteria for reviewing manufacturers' dossiers were agreed. It should be noted that these criteria are intended for use by experts with relevant knowledge and experience in the field of condom manufacturing and clinical trials.

Design

- Is the fundamental design of the product acceptable and suitable for its intended use?

- Are the dimensions of the device appropriate?
- Are the materials selected suitable for the intended use (e.g. biocompatible, lack of toxicity, suitable shelf-life)?
- Are the viral barrier properties of the device specified and have its properties been assessed?
- Are there appropriate mechanisms to retain the device in the vagina and to minimize invagination?
- Does the design generate any special specification and/or testing requirements?
- Has a specific assessment of potential failure modes and other product-specific adverse events been done?
- Has an assessment of risks to the consumer been conducted and are the results reassuring?

Product Specification

- Is the product fully specified (e.g. materials, dimensions, component parts)?
- Is the specification acceptable and suitable for its intended use? (Requirements and criteria that are common to both male and female condoms should be at least as stringent as those specified in ISO 4074:2002)
- Are the tests and acceptance criteria fully described and specified, and appropriate?

Manufacturing and Packaging Process

- Is the factory certified to ISO 13485:2003?
- Is there evidence that the manufacturing process is appropriate?
- Are the quality-control procedures appropriate and reproducible?

Product and Process Validation

- Has the finished product been tested in accordance with parts 5 and 10 of ISO 10993? Has there been an adequate assessment of the results?
- Is there any other specific toxicity testing required?
- Is evidence adequate to justify claims of shelf-life?
- Has the shelf-life been validated?
- Is there evidence of adequate process and equipment validation?

Clinical Evidence

- Is a disease prevention study available for the device?
- Is a contraceptive efficacy study available for the device?
- Is a clinical failure mode study available?
- What clinical failure modes have been considered?
- What are the acceptance criteria for clinical failure modes?
- Are clinical failure mode studies adequate?
- Have product acceptability criteria been considered?

The agreed definitions of female condom failure modes are appended (see Annex 2).

Materials Reviewed

Manufacturers were requested to submit dossiers providing the following information:

- *Material* – safety, toxicity (including allergenic properties), previous use in medical devices, barrier properties, suitability for use with the specific product design, chemical and physical specification, compatibility with lubricants, shelf-life, storage requirements, disposal.
- *Product design* – suitability for pregnancy and STI (including HIV) prevention, reliability, potential failure modes, definition of failure modes, specification, general and specific quality-control requirements, comparative information with respect to other products, documentation on equivalence to marketed products.
- *Manufacturing process* – acceptability of manufacturing process, capacity, reliability of process, control procedures, testing procedures, packaging requirements, process and product validation procedures, validation reports, staffing levels, quality and reliability of equipment, GMP compliance.
- *Quality assurance* – quality manual, procedures, test methods, sample sizes, historical data, process capability studies, use of statistical methods, quality improvement programmes, analysis and use of quality assurance data, frequency of audits, audit outcomes, regulatory and quality system approvals, certification.

- *Clinical data* to support claims of safety, effectiveness and performance, user feedback, product complaints, acceptability studies.
- Other information considered by the manufacturer to be relevant to the assessment.

The Female Health Company, United Kingdom, and Medtech Products Limited, India, submitted complete dossiers on their products. Natural Sensation Compania Ltda, Colombia, submitted information on the product design, but was not in a position to submit a full dossier. Given the limited information submitted by Natural Sensation Compania Ltda, this particular product was not reviewed in detail.

Conclusions and Recommendations

The *Female Condom Technical Review Committee* was impressed by the quality of the work being undertaken and the innovative nature of the products under development. The Committee considered that these new products may provide women and couples with greater choice of barrier methods, particularly if they can be made available for public-sector procurement and social marketing programmes. The *Female Condom Technical Review Committee* made the following recommendations:

1. In order to assess the safety and efficacy of a female condom design, a clinical efficacy study is strongly recommended. This should take the form of a contraceptive efficacy study. However, adequately powered clinical failure mode studies may be acceptable if the new device is sufficiently similar in design and specification to a marketed device and comparative clinical failure mode studies support a claim of equivalence.
2. A set of review criteria (design, specifications, manufacturing, product and process validation and clinical data) were developed for the assessment of safety and effectiveness of female condoms. It is recommended that these review criteria are used by experts for conducting future assessments of female condoms.
3. A set of definitions for clinical failure modes of female condoms has been developed. It is recommended that these

general definitions be harmonized with the definitions in the draft ISO Female Condom Standard and used in future clinical studies. The general definitions may need to be supplemented by product-specific failure mode definitions for certain designs (see Annex 2).

4. The Committee considered the possibility of producing a generic specification for female condoms, but decided that, in view of the uniqueness of each design, and the differences between them, such a specification is impractical at present.
5. Confidential reports were submitted to each manufacturer with a request that further information be provided to the technical experts in order to clarify the issues raised during the technical review process.
6. The technical experts agreed to review in accordance with the agreed criteria any additional material submitted by manufacturers in response to the confidential reports issued by the *Female Condom Technical Review Committee*. The WHO Department of Reproductive Health and Research would coordinate this ongoing review process and be responsible for collating the recommendations of each technical expert and responding to the manufacturer.
7. In the case of one manufacturer this review process was completed in December 2006.

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Standardized definitions for failure modes of female condoms

(Annex 2)

Discussed and finalized in collaboration with key stakeholders and members of Female Condom Working Group of the International Standardization Organization, Technical Committee 157 responsible for the preparation of the International Standard for Female Condoms, December 2006.

Definitions of Failure Modes

1. Definition of the female condom

The *Female Condom Technical Review Committee* adopted the following working definition of the female condom:

Female condom: a device that is designed to be used by the woman to prevent pregnancy and/or sexually transmitted infections during vaginal intercourse. It is distinguished from a male condom by being retained in the vagina after insertion. The external component of the device usually provides some protection to the external female genitalia.

2. Working definitions of failure modes

The definitions of failure modes below were agreed by the *Female Condom Technical Review Committee* and apply to female condoms currently marketed or in advanced stages of clinical testing, and may be relevant to other devices under development. The definitions are designed to assist in the review and comparative assessment of different female condoms. However, since the failure modes may be design-specific, there may be special characteristics of a device that require the definitions of failure modes to be adapted, or new failure modes defined.

Non-Clinical Breakage: Breakage without adverse clinical consequences

Non-Clinical Breakage is defined as breakage noticed before intercourse or occurring after withdrawal of the condom from the vagina. Non-clinical breakage is breakage without potential adverse clinical consequences. The **non-clinical breakage rate** is calculated by dividing the number of female condoms noted to have broken before intercourse or after withdrawal by the number of female condom packages opened.

Clinical Breakage: Breakage with potential adverse clinical consequences

Clinical Breakage is defined as breakage during intercourse or withdrawal of the female condom from the vagina. Clinical breakage is breakage with potential adverse clinical consequences. Clinical breakage includes events where the outer frame or ring breaks. The **clinical breakage rate** is calculated by dividing the number of female condoms reported to have broken during intercourse or withdrawal by the number of female condoms used during intercourse.

Total Breakage is defined as female condom breakage at any time before, during or after intercourse. It includes clinical breakage and non-clinical breakage. The **total breakage rate** is calculated by dividing the total number of female condoms that broke by the number of female condom packages opened.

Slippage is defined as a female condom that slips completely out of the vagina during intercourse. The **slippage rate** is calculated by dividing the number of female condoms that slipped completely out of the vagina by the number of female condoms used during intercourse.

Misdirection is defined as vaginal penetration whereby the penis is inserted between the female condom and the vaginal wall. The **misdirection rate** is calculated by dividing the number of reported events of misdirection by the number of female condoms used during intercourse.

Please note:

Misdirection may be difficult for the woman or her partner to notice and there is a risk that it may be underreported in studies. Additional studies using, for example, substantial increases in prostate-specific antigen levels in vaginal secretions following intercourse, or other markers of potential exposure to semen or seminal fluid, may be an additional useful measure where the design of the device makes misdirection an important potential failure mode.

Invagination is defined as part or the entire external component of the female condom being pushed into the vagina during intercourse. The **invagination rate** is calculated

by dividing the number of events of invagination by the number of female condoms used during intercourse.

Please note:

While some authors distinguish between **partial invagination** and **complete invagination**, the distinction is considered of minor importance because the protection afforded by the female condom to the external genitalia will be compromised if any of the external portion of the device is pushed into the vagina.

Total Clinical Failure is defined as the number of female condoms that clinically break or slip, or are associated with misdirection or invagination, during intercourse or any additional failure mode(s) identified in the risk assessment. The **total clinical failure rate** is calculated by dividing the number of female condoms with a clinical failure by the number of female condoms used during intercourse.

A Condom Failure is defined as a condom for which a non-clinical breakage, a clinical breakage or a slippage occurs, or is associated with misdirection or invagination or any additional failure mode(s) identified in the risk assessment. The **condom failure rate** is calculated as the number of condoms that fail divided by the number of female condom packages opened.

NB. It is recommended that individual and combined failure rates are reported not only per condom used or condom packages opened, but also per user.

The Working Group of the International Organization for Standardization responsible for formulating the international standard for female condoms (ISO/TC/157/Working Group 20) reviewed and agreed to use these definitions in the Standard. They did, however, recommend that the standardized definitions should also include the following:

The manufacture should define other failure mode(s) identified during the risk assessment. All failure modes must be considered in the design of any preclinical or clinical investigations of the female condom.