World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO/UNFPA
Female condom generic specification

Please send your comments to **Dr Steve Estevão Cordeiro**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (estevaos@who.int), with a copy to Mrs Bezawit Kibret (kibretb@who.int; nsp@who.int) before **30 January 2023.** Please use the "Table of Comments" document for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects) for comments under the "*Working documents in public consultation*" link. If you wish to receive all our draft guidelines, please send your email address to nsp@who.int and your name will be added to our electronic mailing list.

SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/22.913:

WHO/UNFPA
Female condom generic specification

Description of Activity	Date
Preparation of first draft working document	July 2022
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	July 2022
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	September 2022
Discussion of the feedback received on the working document in a virtual meeting with an expert working group.	October - November 2022
Preparation of working document for next round of public consultation.	December 2022
Mailing of revised working document inviting comments, including to the EAP, and posting the working document on the WHO website for a second round of public consultation.	December 2022
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	February -March 2023
Discussion of the feedback received on the working document in a virtual meeting with an expert working group.	June - July 2023
Presentation to the Fifty-seventh meeting of the ECSPP.	October 2023
Any other follow-up action as required.	

WHO/UNFPA
Female condom generic specification

1. Introduction

This annex contains the World Health Organization (WHO)/United Nations Population Fund (UNFPA) specification for female condoms that is suitable for the bulk procurement of female latex condoms for use in social marketing, public-sector programmes for family planning and the prevention of sexually transmitted infections.

Whereas a standard usually specifies the minimum requirements for the key properties that determine the safety and effectiveness of a product, a specification is a statement of the buyer's requirements and covers all the attributes and features of the product. Some of these requirements, such as packaging and labelling, may be unique to the buyer and not specified in the International Organization for Standardization (ISO) standard ISO 25841 *(1)*.

The WHO/UNFPA specification is based on the performance requirements for female condoms specified in the international standard ISO 25841*, Female condoms: requirements and test methods*. This standard, which was developed by the ISO Technical Committee responsible for developing standards for barrier contraceptives, *ISO/TC 157*, was first published in July 2011. The standard has subsequently been updated to reflect the introduction of new types of female condom designs and changes in the availability of control condoms for conducting clinical studies. This updated standard was published as *ISO 25481:2017(1)*. An amendment to the standard, ISO 25841:2017/Amd.1:2020 *(2)*, was published in 2020. The amendment includes verification procedures for assessing the effectiveness of the test procedures for package integrity and freedom from holes. The current edition of the standard at the date of publication of this specification is ISO 25841:2017+A1:2020 *(2)*.

Throughout this specification reference to ISO 25841 (*1*) will refer to the latest edition of the standard. No significant changes to *25841*:2017/Amd.1:2020 *(2)* are expected until at least 2025.

Many potential designs of female condom are possible, each with its own set of design parameters and specifications. A wide range of materials can also be used to make female condoms. It is therefore not possible to establish a set of performance requirements for female condoms in the same way as it is for male latex condoms. Certain performance properties, such as burst volume and pressure, will depend upon the materials used and the design of the condom. These properties will therefore vary with condom type and design. Other performance properties, such as acceptance limits for freedom

from holes, are independent of the materials and designs used. Specific limits can be set for these requirements. Whenever possible, specific limits have been set in this document.

Female condoms also have a number of essential features that are not found on male condoms. In general terms, female condoms usually have the following components:

1. A sheath that lines the vagina and may extend to cover or partially cover the external genitalia.
2. An external retention feature that prevents the condom from being pushed into the vagina. Commonly this is a ring or frame.
3. An internal retention feature that retains the condom within the vagina and permits safe withdrawal of the penis after use. Examples include rings, foam sponge devices and mucoadhesive tabs.
4. A product insertion feature that facilitates insertion of the condom into the vagina. The internal retention feature may also serve this function.

For the reasons given above, it is not possible to determine the safety, efficacy, and acceptability of a specific type of female condom based on its design and the materials used. Instead, it is necessary to conduct clinical investigations in humans to confirm the safety, efficacy and acceptability of any new female condom design. These investigations enable an assessment of the overall performance of internal and external retention features, failure modes, safety and effectiveness of female condoms to be made.

ISO 25841 *(1)* specifies the essential performance and safety requirements that female condoms are expected to meet and the test methods that are used to assess compliance with these requirements. It is based on extensive research and an ongoing consultation process involving leading experts in all aspects of female condom manufacturing, research and use from around the world.

Each design of the female condom will have unique features that also may need to be agreed upon between the buyer and manufacturer. The buyer's specification must be a detailed and unambiguous statement of the buyer's requirements describing how those requirements can be measured and assessed. The specification is generally attached to the bidding documents and forms which are part of the supply contract. It is premature to develop a design-based specification for the public sector procurement of female condoms. Many different designs of the product are possible, each having its own unique features and specification. As a result, it has been decided to detail the scientific and

technical requirements manufacturers must meet to be approved for public sector distribution. These requirements incorporate the design and performance requirements of ISO 25841 *(1)*.

This specification covers the generic requirements for female condoms and is largely performance based. For this reason, it is known as the WHO/UNFPA *Female condom generic specification*. The *WHO/UNFPA Female condom generic specification* has been developed by consensus and is based on available evidence, the details of which are catalogued in a technical basis paper. This generic specification describes the general, design, performance and packaging requirements for the product and the methods of verification. Female condoms are made and tested in lots. A lot is a collection of female condoms of the same design, colour, shape, size and formulation manufactured at essentially the same time using the same process, same specification of raw materials, common equipment, same lubricant and any other additive or dressing and the same packaging materials. Further information about lots is given in Table 1.

The requirements have been divided into four categories as follows:

- **General requirements** specify the clinical performance requirements of the product; the methods to be used by the manufacturer to set the product specifications for airburst properties; and the safety of constituent materials and other characteristics, such as shelf life. These requirements and properties should not vary from lot to lot and therefore do not need testing on a regular basis.
- **Performance requirements** specify the essential performance attributes of the condoms. These must be tested on a lot-by-lot basis since the quality of these attributes may vary due to the manufacturing process. Laboratory tests are conducted to ensure that the condom and the individual packages comply with the specification. Performance requirements detailed in this specification should not be changed. The Performance requirements are listed in Section 3.2 of this document.
- **Design requirements** are concerned with the acceptability of the product to the end user. They are listed in Section 3.3 of this specification. Some of these properties may be varied within certain limits to meet specific programmatic requirements by agreement with the manufacturer. Unlike the situation with male condoms, however, varying a design requirement might affect the clinical effectiveness of the female condom. Since the performance and acceptability of female condoms are established by clinical investigation, the potential impact of any change must be considered carefully. Such changes are therefore

not generally feasible and users should choose from amongst the approved, available designs. For each design requirement, there is a means of verification. **Packaging requirements** are listed in Section 3.4 of this specification. If appropriate, purchasers may specify specific requirements depending upon the target population. When selecting packaging, manufacturers should consider the needs of disabled users. If consumer packaging is required, it is important to include detailed instructions in the specification and to discuss the design requirements with the manufacturer.

The WHO/UNFPA Female condom generic specification and the WHO/UNFPA Prequalification Programme guidance are designed to ensure that a quality-assured product is purchased and distributed to the end user. This WHO/UNFPA specification should not be considered nor used as a standard for regulatory purposes. For regulatory purposes, the applicable standard is ISO 25841 *(1)* or the relevant local standard, depending on the country.

2. Glossary

acceptance quality limit (AQL). The quality level that is the worst tolerable process average when a continuing series of lots is submitted for acceptance sampling (*ISO 2859-1*). *Note*: Manufacturers should be consistently achieving a process average that is better than the AQL.

aseptic technique. Precautionary measures taken to prevent external contamination of materials, samples and culture media, employed during testing.

ATP. Adenosine triphosphate.

batch. Sometimes used in place of “lot” (see definition of lot; WHO recommends that “lot” be used when referring to condoms). It can also refer to a homogenous quantity of latex that has been compounded and is ready for dipping, from which several lots will be made, or describe a quantity of individual raw materials.

bioburden. The population of microorganisms on a raw material, a component, a product, packaging or equipment.

bioluminescence. When bacterial adenosine triphosphate reacts with firefly luciferin and luciferase, light is emitted. Bioluminescence tests are designed to measure the amount of light produced which will be related to the number of microorganisms present in the sample.

CE mark. On condom packaging, a mark certifying that the product conforms to the essential requirements of the European Medical Device Regulation ({EU} 2017/745).

colony forming unit (cfu). An estimate of the number of viable microorganisms per unit measured.

CI. Confidence interval.

compliance testing. A regime of testing to verify that a lot complies with the specification.

consumer pack. A wallet or carton into which one or more individual packages are inserted for marketing purposes.

design requirements. Characteristics of the condom that are specified according to the buyer's requirements.

expiry date. The date by which the product is no longer considered acceptable for use.

exterior shipping carton. The container into which a number of inner boxes are packed.

FDA. United States Food and Drug Administration.

forecast. An assessment of the future requirements of a programme, based on historical trends, research or feedback from fieldworkers on current needs.

general requirements. The general quality characteristics of condoms that are verified before supply commences and that are not expected to vary from lot to lot.

good manufacturing practice (GMP). A code of practice aimed at ensuring that the product is consistently manufactured to the required standard.

HIV. Human immunodeficiency virus.

inner box. A box used to contain a convenient number of condoms in packages or consumer packs. Inner boxes will typically be presented as dispenser boxes containing one hundred condoms.

inspection level. The degree of examination of the lot, as specified in *ISO 2859-1*. The higher the inspection level, the more samples will be tested, and hence the lower the risk of faulty products reaching the end user.

ISO. International Organization for Standardization.

ISO/TC 157. International Organization for Standardization, Technical Committee 157 for non-systemic contraceptives and sexually transmitted infection (STI) barrier prophylactics.

length. The length of the condom measured from the open end to the tip, excluding any reservoir.

lot. A quantity of condoms of a single grade, class, size and composition, manufactured under essentially the same conditions. With certain exceptions, all the condoms constituting a lot will have identical formulation (the same dimensions, colour, shape and surface texture), be manufactured on the same production line and be vulcanized under the same conditions.

lot number or code. A unique identifying alphanumeric code assigned to a lot.

lowry method (modified). A method for determining the water-extractable protein levels in latex products.

MDR. Medical Device Regulation ((EU) 2017/745).

MFV. Maximum fill volume (for water testing for freedom from holes).

MSDS. Material safety data sheet.

national regulatory authority. A regulatory body with authority in a specific country to control the importation and distribution of medical products. See the definition of regulatory authority.

performance requirements. The critical tests of quality that all lots must pass to provide adequate consumer protection.

prequalification. The steps taken by the buyer to verify a manufacturer's suitability to provide condoms of the required quality. The WHO/UNFPA Prequalification Programme includes the periodic assessment of manufacturing dossiers, testing of samples and factory inspection.

pre-shipment compliance testing. A regimen of compliance tests conducted before a shipment leaves the supplier's factory.

process average. The long-term average percentage of non-complying condoms calculated separately for each attribute. Ideally, the process average for a specific attribute should be less than half the specified acceptance quality limit (AQL).

regulatory authority. A national or international body set up to oversee the safety, efficacy and quality of medical devices, including condoms, imported and distributed within a country or region.

rejection number. The minimum number of non-compliers (failures) in a test sample that will cause a lot to be rejected.

reservoir. A narrow portion of the condom at the closed end, designed to contain ejaculate. The reservoir is sometimes called the teat.

sampling plan. A specific plan that indicates the number of units (condoms) from each lot that are to be inspected (sample size) and the associated criteria for determining the acceptability of the lot (acceptance and rejection numbers).

SE. Standard error.

shelf life. The period of time after manufacture during which the product is considered acceptable for use.

specification. A detailed statement of a product's requirements as established by the buyer. Usually, a specification is based on an established standard.

standard. A detailed statement of the minimum acceptance requirements, as established by a national or international regulatory authority.

STED. Summary of technical documentation.

STI. Sexually transmitted infection.

Surrogate virus. A virus that is safer and easier to handle, and can be used as a substitute for a pathogenic virus.

UNFPA. United Nations Population Fund.

viscosity. A fluid's resistance to flow.

WHO. World Health Organization.

3. WHO/UNFPA specification

3.1 General requirements

General requirements include the selection and safety of materials used to manufacture the condom and any insertion and retention devices. Manufacturers shall include, in their summary of technical documentation (STED), documentary evidence to confirm that the condoms comply with the requirements listed in Tables 1–4. Verification of conformance to these requirements is assessed during prequalification and in response to any purchaser's doubts about whether or not the product complies with the WHO/UNFPA female condom generic specification.

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326 Manufacturers are also required to include data in their STEDs supporting the shelf life claims made
327 for the product. Female condoms must comply with the performance requirements specified in
328 Section 3.2 of this WHO/UNFPA female condom generic specification throughout the stated shelf life
329 of the condom. Manufacturers must determine the shelf life with real-time studies conducted at
330 (30^{+5}_{-2})°C. Pending the outcome of real-time studies, manufacturers may use appropriate accelerated
331 studies to estimate a provisional shelf life. The basis used to estimate the provisional shelf life from
332 the accelerated data must be explained in the product dossier and the appropriate validation data
333 must be included.

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Table 1. General requirements (to be included in the STED and verified during prequalification)	
Clinical investigation report	Copies of clinical investigation reports shall be made available for review and included in the product dossier. The reports shall clearly identify the product variant to which they relate. Any changes made to the product since the clinical investigation was completed shall be documented. If a comparative clinical investigation against a marketed female condom has been conducted, the reports shall clearly identify the marketed female condom, including its manufacturer, the date of manufacture (if known) and the expiry date of the samples used in the study. The report shall include the test results for the condoms used in the trial, including burst test results.
Specification for minimum burst pressure and volume	Copies of reports relating to the setting of minimum burst pressure and volume specifications shall be made available and included in the product dossier. Reports shall include the original burst data on the lot(s) of condoms used in the clinical investigations and details of how the minimum limits for burst pressure and volume were established. If the burst requirements are not based on the lot(s) of condoms used in the clinical investigations, then a full justification is required to establish equivalence between the condom lot(s) used to set the specification and those used in the clinical evaluation.
Data sheets	Copies of the most recent data sheet giving the manufacturer's specification for the product, as defined in Section 1.5, shall be included in the product dossier.
Lot definition	A lot is a collection of condoms of the same design, colour, shape, size and formulation. A lot must be manufactured at essentially the same time, using the same process, same specification of raw materials, common equipment, same lubricant and any other additive or dressing, and be packed in the same type of individual container, using the same packaging materials. All condoms comprising a lot will: • have an identical formulation; • have the same design, dimensions, colour, shape and

Table 1. General requirements (to be included in the STED and verified during prequalification)	
	surface texture; • be manufactured on the same production line; • be vulcanized under identical conditions; • be in the same packaging; • have the same lubricant; and • have the same date of expiry printed on the package. Lot sizes over 500,000 are not permitted.
Materials	The condoms, retention features and any other components, such as insertion features, shall be made of suitable materials, as specified by the manufacturer. If significant changes are made to the grade or type of materials used, then the manufacturer may be required to repeat one or more of the safety, clinical and stability assessments of the product. Full details of the materials shall be given, including, if appropriate, polymer and copolymer compositions. Additional information about the material used for the sheath shall be given, including its key physical properties (tensile strength and modulus). For thermoplastic elastomers, the molecular weight and molecular weight distribution shall also be given.
Barrier properties	The barrier properties of the female condom shall be established by viral penetration studies using a suitable surrogate virus, for example bacteriophage phi X174. When tested in accordance with the method given in ISO 25841 *(1)*, the volume of virus-containing medium penetrating the condom shall not exceed twice the limit of detection of the test for at least 80% of the condoms tested. A marketed male latex condom that complies with the requirements of ISO 4074 *(3)* may be used as a control in the study. For condoms made from natural rubber latex with a sheath that has a minimum thickness of 0.055 mm and is made using conventional latex-dipping processes, an exception from barrier testing is permissible since the barrier properties of such films in relation to viruses are well established. This exemption does not apply if the sheath is made using unusual dipping or vulcanization technology, if the sheath component or the finished condom is subjected to any subsequent treatment process other than washing, or if any additive other than the usual vulcanization ingredients and stabilisers is added to the latex. Confirmation of the viral barrier properties of the condom is normally completed prior to the submission for regulatory approval for the product. If any changes are made to the condom that could affect the barrier properties of the condom, for example changing the material used for the sheath component, the viral barrier test shall be repeated.
Biocompatibility	The condoms shall not liberate toxic or otherwise harmful substances in amounts that can be irritating, sensitizing or otherwise harmful to the user of the condom under normal conditions of use. Biocompatibility assessments shall be conducted on the whole condom, including the retention devises, any insertion device that might come into

Table 1. General requirements (to be included in the STED and verified during prequalification)	
	contact with the vagina and any lubricants and dressing materials, in accordance with ISO 10993-1 *(4)*. Generally, tests for cytotoxicity shall be conducted in accordance with ISO 10993-5 *(5)* and tests for irritation and sensitization shall be conducted in accordance *with* ISO 10993-10 *(6)*. Manufacturers should choose accredited laboratories for these tests, and the results should be interpreted by an accredited toxicologist or other suitably qualified expert. In accordance with ISO 10993-1 *(4)*, manufacturers may use existing data on identical materials instead of conducting their own tests. Expert reports shall be available for review. If there is a likelihood of systemic absorption of any components or residuals, further biocompatibility testing may be requested by regulatory authorities, such as testing for acute systemic toxicity in accordance with ISO 10993-11 *(7)* and testing for mutagenicity in accordance with ISO 10993- 3 *(8)*. The manufacturer shall also obtain, and make available on request from regulatory authorities, toxicity data on all the additives and residual monomers, solvents and known impurities used in the manufacture of the female condom. Suitable material safety data sheets (MSDSs) shall be supplied on request for materials used in the manufacture of the condoms, retention features and lubricant. Regarding female condoms made from natural rubber latex, many latex products that have been established as safe, including male condoms and medical gloves, can exhibit a positive cytotoxic response when tested in accordance with *ISO 10993-5 (5)*. Although any cytotoxic effect can be of concern, it is primarily an indication of potential for in vivo toxicity, and a female condom cannot necessarily be determined to be unsuitable for use based solely on cytotoxicity data. Manufacturers and/or the purchasers are advised to confirm local requirements for safety testing with appropriate regulatory authorities in the countries in which the condoms are to be distributed.
Water-extractable protein levels	It is recommended that manufacturers of natural rubber latex-based female condoms determine the water-extractable levels of proteins in their products. The recommended level for soluble protein, as determined by the modified Lowry method, is less than 200 µg/g. Manufacturers should take steps not to exceed this level and should monitor production periodically. There is no specific standard for determining the protein levels in condoms. The methods described in ISO 12243 *(9)* , EN 455–3 *(10)* and ASTM D5712 *(11)* for determining the protein levels in medical gloves can be modified for condoms. Documentation recording protein levels should be available for review.
Bioburden levels	Condoms are not sterile devices but manufacturers should take steps to minimize the risk of contamination of the products with microorganisms. Some

Table 1. General requirements (to be included in the STED and verified during prequalification)	
	designs of female condoms may increase the risk of microbiological contamination because of the materials used and the additional manipulation required to assemble the finished device. It is recommended that bioburden levels on packed condoms are below 100 cfu and should not be allowed to exceed 500 cfu. There should be an absence of *Staphylococcus aureus* and *Enterobacteriaceae*, including *Escherichia coli*, *Pseudomonas aeruginosa* and all fungi. It is recommended that bioburden levels be determined periodically (e.g. at least quarterly) by extracting the condoms with a neutralizing medium and determining the total viable aerobic count using appropriate test methods. Further information on the rationale for the bioburden limits, methods of determining bioburden levels and general guidelines on controlling bioburden contamination during manufacture is given in ISO 25841 *(1).* Confirmation that bioburden levels are below 500 cfu/condom will be assessed for lots of condoms submitted for prequalification testing.
Nitrosamines	Manufacturers of latex-based female condoms should take steps to minimize the formation of nitrosamines. This can be done by ensuring that condoms are adequately leached and washed by using minimum amounts of accelerators and by choosing accelerators, such as zinc dibutyldithiocarbamate, that have a preferred safety profile. [1] For prequalification purposes, the manufacturer should be able to demonstrate they are able to achieve levels below 50 ppb (parts per billion) measured as per *ISO 29941 (12).* Levels should be monitored periodically, at least once a year, and following any significant change to the latex formulation.
Aromatic amines	Manufacturers using polyurethanes shall confirm that aromatic amines cannot be leached out of the female condom at levels that could be considered toxic.
Shelf life	Condoms shall conform with the performance requirements of this WHO/UNFPA female condom generic specification throughout the stated shelf life of the condom. The manufacturer shall determine the shelf life based on the outcome of stability studies determined from the date of manufacture. The date of manufacture can be the date of sheath manufacture or the date of assembly and packaging of the female condom in individual sealed containers, depending on the procedures specified by the manufacturer. The date of manufacture shall not exceed six months from the date of sheath manufacture.

[1] J. Tinkler, D. Gott and J. Bootman, "Risk assessment of dithiocarbamate accelerator residues in latex-based medical devices: genotoxicity considerations", *Journal of Food Chemistry and Toxicology*, vol. 36, Nos 9–10 (1998), pp. 849–866.

Table 1. General requirements (to be included in the STED and verified during prequalification)	
	Unprocessed sheaths and/or unpackaged female condoms shall be stored under controlled conditions, as specified by the manufacturer between sheath manufacture and packaging. Manufacturers shall have documented procedures for validating the storage conditions and maximum storage period. The stored sheaths and/or female condoms shall be protected from exposure to excessive temperatures, light, ozone and anything else that could affect the shelf life of the packaged female condoms. The claimed shelf life shall be not less than three years and no more than five years, subject to confirmation by the appropriate stability data. For WHO/UNFPA prequalified manufacturers, the maximum period of time between sheath manufacture and assembly/packaging is 6 months but manufacturers may use shelf life data from stability studies with condoms that have been stored up to two years prior to packaging as specified by ISO 25841 *(1)* to support shelf life claims. Manufacturers must commence real-time studies before lodging their applications for prequalification. Pending the outcome of the real-time studies, manufacturers may estimate a provisional shelf life using an accelerated ageing study. If, at any time during the real-time studies, the manufacturer becomes aware that the shelf life estimates made using the accelerated studies are incorrect, the manufacturer must notify UNFPA and the purchasers immediately.
Stability studies-real time	Shelf life shall be confirmed by real-time stability studies conducted at 30 (+5/-2) °C according to the relevant clause in ISO 25841 *(1)*. If the condom or any critical components, such as the retention features, are made from moisture-sensitive materials, and a moisture-impermeable packaging material is not used, then relative humidity shall be controlled at (75 ± 5) % during real-time stability studies. For confirmation, humidity control is not required when conducting stability studies on female condoms made from natural rubber latex packed in impermeable packaging Details about the methods of determining the shelf lives of female condoms are given in ISO 25841 *(1)*. If the female condom sheath is made from natural rubber latex by conventional dipping processes and the female condom is packed in an oxygen impermeable individual container, for example, made from aluminium foil laminate, then the procedure used to determine a provisional shelf life of natural latex male condoms described in ISO 4074 *(3)* can be used. For female condoms with sheaths made out of synthetic materials, the procedures described in *ISO 11346* (*Rubber, vulcanized or thermoplastic: estimation of lifetime and maximum temperature of use*) *(13)* may be appropriate. The procedures used for accelerated stability studies shall be appropriate to the raw materials of the condom.

Table 1. General requirements (to be included in the STED and verified during prequalification)	
	The results of an accelerated aging study, according to ISO 25841 *(1)*, must be available at the time of submitting an application for prequalification and a real-time study must also be in progress.
Sampling	Condoms for stability studies shall be taken from three normal production lots. Sampling shall be done according to Annex A or Annex B (preferred) of ISO 25841 *(1)*. The sample sizes from each lot should be adequate to complete all the tests specified in Annexes L and M of ISO 25841 *(1)* and include sufficient samples to permit retesting in full after at least one addition time point during the studies.
Conditioning	Samples shall be conditioned in their individual sealed containers according to the relevant annex of ISO 25841 *(1)*. At the end of the incubation periods, withdraw the condoms and test for airburst properties, freedom from holes and package seal integrity.
Testing requirements	For real-time stability studies, all three lots of condoms shall conform to the requirements for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 25841 *(1)* for the full specified shelf life of the product. For accelerated studies, suitable means of extrapolation shall be used to support the specified shelf life.
Stability study reports	The stability study reports should indicate the time between sheath manufacture and assembly/packaging for the lots used for the study. If a manufacturer has not recorded the required information in the stability study report, then the default position will be that the manufacturer must use the sheath manufacturing date as the date of manufacture.
Individual container	The individual container shall not adversely affect the properties of the female condom. The individual container shall be sealed and shall provide an adequate level of protection consistent with the materials used to manufacture the condom. The individual container shall not allow lubricant to leak. Individual containers for female condoms made from natural rubber latex, or other materials that can be affected by light, shall be opaque. It is unlikely that biodegradable packaging will provide sufficient product protection for female condoms made from natural rubber latex. The individual containers shall have sufficient mechanical strength to protect the condoms during shipping and storage. Purchasers may choose to specify special packaging requirements at the purchase order stage, in which case the requirements must be included in the purchase specification.

3.2 Performance requirements

The performance requirements specified here are based on the requirements in the current published edition of ISO 25841 *(1)*. These requirements cannot be altered. Verification of compliance with these requirements must be done as part of the prequalification process and the lot-by-lot pre-shipment compliance testing of the product.

For prequalification purposes (i.e. when testing fewer than five lots), the sampling plans specified in Annex B of ISO 25841 *(1)* shall be used. For lot-by-lot compliance testing, (i.e. when testing continuing series of lots) the sampling plans specified in Annex A of ISO 25841 *(1)* shall be used. Sample requirements for testing are summarised in Appendix I.

Table 2. Performance requirements	
Bursting volume and pressure	
Sampling	In accordance with *ISO 2859-1* General Inspection Level I *(14)* . For prequalification testing, at least Code Letter M as specified in Annex B of ISO 25841*:2017 (1)* shall be used.
Testing	In accordance with the method given in the relevant annex of ISO 25841 *(1)*. Condoms shall comply with the minimum burst volume and pressure requirements specified by the manufacturer, as determined according to the method described in Table 3.
Requirements	The limit for non-conforming condoms is an AQL of 1.5.
Freedom from holes and visible defects, including critical visible defects in packaging	
Sampling	*ISO 2859-1* General Inspection Level I *(14)* but at least Code Letter M shall be used. For prequalification testing, at least Code Letter N as specified in Annex B of ISO 25841*:2017 (1)* shall be used.
Testing	Condoms shall be assessed in accordance with the method given in the relevant Annex of ISO 25841 *(1).* Critical visible defects in the individual containers are also assessed at the same time using the same samples. The list of critical and noncritical visible defects for the condoms and individual containers is given Appendix II
Requirements	The limits for non-conforming condoms are: • freedom from holes: AQL 0.25 • critical visible defects: AQL 0.4 • non-critical visible defects: AQL 2.5 The limit for non-conforming individual containers is an AQL of 0.4. Condoms having holes within 25 mm of the open end found by the water test but not observed when the condoms were inspected prior to being filled with water (non-visible holes) are counted as conforming.

Table 2. Performance requirements	
	Descriptions of critical visible defects and non-critical visible defects are given in Section 4. Exact definitions of critical and non-critical defects should be reviewed and agreed on during the contractual process.
Package integrity (seal integrity)	
Sampling	*ISO 2859-1* Inspection Level S-3 *(14)* . For prequalification testing, at least Code Letter H as specified in Annex B of ISO 25841*:2017 (1)* shall be used.
Testing	In accordance with the method given in the relevant annex of ISO 25841 *(1).*
Requirements	The limit for non-conforming individual containers is an AQL of 2.5.

3.3 Design requirements

Since the approval of female condoms is based on a satisfactory outcome from the clinical investigation, any change in the design of the condom or the materials used requires a detailed evaluation to ensure that the safety and effectiveness are not compromised. A full risk assessment using, for example, the procedures described in *ISO 14971 (15)* shall be conducted following any significant change to the design, formulation, manufacturing process, equipment used and packaging. As a consequence of the risk assessment, further clinical investigation of the product and/or retesting may be required. The design of the condom must not be changed from that used in the clinical investigation without consultation and approval from UNFPA.

For the design requirements listed in Table 3, the nominal specified requirements shall be the same as those for the samples of condoms submitted for clinical investigation. All condoms tested in the sample shall fall within the tolerances specified for the specified mean nominal value. Any variation in the specified tolerances may be acceptable at the time of prequalification, subject to a full justification for the variation and agreement with UNFPA.

Table 3. Design requirements	
Sampling	Unless otherwise stated all design requirements shall be assessed using a sample size of 13 female condoms.
Requirements	Unless otherwise stated all samples shall conform to specification
Essential features	
Verify by visual inspection	A female condom will normally have the following essential features: 1. A sheath component that lines the vagina and may extend to cover or partially cover the external genitalia.

	2. An external retention feature to prevent the condom from being pushed into the vagina. Commonly this is a ring or a frame. 3. An internal retention feature that retains the condom within the vagina and permits safe withdrawal of the penis after intercourse. Examples include rings, foam sponge devices and mucoadhesive tabs. 4. A product insertion feature that facilitates insertion of the condom into the vagina. The internal retention feature may also serve this function.
Minimum burst properties	The minimum burst volume and pressure for the condom shall be based on results obtained by testing at least 2000 female condoms from the lot or lots used in the clinical trial (if more than one lot was used the samples shall be drawn across all lots in proportion to the size of each lot). The minimum burst pressures and volume limits shall be set at 80 % of the 1,5 percentile values of the measured airburst volumes and pressures. Round the bursting volume limit to the nearest 0,1 dm^3 if the value is 14,9 dm^3 or below and to the nearest 0,5 dm^3 if the value is greater than 14,9 dm^3. Round the bursting pressure to the nearest 0,05 kPa. After a period of essentially continuous production of at least 30 full scale manufacturing lots, the limits should be re-evaluated to confirm that they are still applicable.
Requirements	All condoms in the sample shall have the essential features and components specified by the manufacturer, which shall be the same as those for the condoms used in the clinical investigation. These requirements include: • the materials used for the sheath and all retention features; • the method of manufacture of the female condom in including the sheath and the retention features; • the dimensions of the sheath and retention features; • the physical properties of the materials used for the sheath and retention features; and • the type and amount of lubricant used. If any of these critical design requirements are changed for any reason, a full risk assessment must be completed to demonstrate that the safety and effectiveness of the product has not been compromised. A further clinical investigation may be necessary to confirm this.
Colour	
Pigments	If any pigment is used to colour the condom, it shall be suitable for use in medical devices. Full details of any pigments used shall be supplied along with the relevant MSDS.
Colour assessment	Sample of female condoms from each lot shall be inspected visually for colour (colour may be assessed on the same sample of condoms used to assess other design requirements). Reference samples or colour charts may be used to define and assess colour. Exact colour matches may not be possible.
Odour and flavour	

Verify by visual inspection and smell	The condoms shall not give off an unpleasant odour when the package is opened at any time after manufacture and during the shelf life of the product. (Many materials, including natural rubber latex, have a characteristic odour. Often the odour tends to dissipate quickly once the package is opened. A mild odour that dissipates quickly is acceptable.) It is suggested that appropriate reference samples be retained by the testing laboratory to help resolve disputes over odour. It is recommended that the retained samples be kept for the duration of the shelf life of the condom. Purchasers may, by agreement with the manufacturer, specify the addition of a suitable fragrance and/or flavour. Such fragrances and flavours must be non-toxic and non-irritant and not adversely affect the performance and acceptability of the condom. If a fragrance or flavour is included, full details of the fragrance or flavour, including an MSDS, shall be included in the STED and Data Sheet.
Testing	See Appendix III for guidance on odour testing. If a masking agent or fragrance is used, odour testing should become part of the lot-by-lot pre-shipment compliance testing. Odour testing should be included in ageing studies. Evaluation of odour is inherently subjective, and a degree of tolerance is required when assessing products for conformance with the specification.
Width	
Testing	Samples from each lot shall be assessed in accordance with the method given in the relevant Section of I*SO 25841 (1)*. The width of a female condom is unique to each design. The manufacturer shall specify the nominal width of female condoms at each of the measurement locations given in the relevant Annex of ISO 25841 *(1).* The maximum tolerance for width requirements shall be ±2 mm around the specified width.
Length	
Testing	Samples from each lot shall be assessed in accordance with the method given the relevant Annex of ISO 25841 (*1).*
Requirements	The length of a female condom is unique to each design. The manufacturer shall specify a nominal length for the female condom consistent with the length of the female condoms used in the clinical investigation. The maximum tolerance shall be ±5 mm if the nominal length is 150 mm or less and ±10 mm if the nominal length is greater than 150 mm.
Thickness	
Testing	A sample from each lot shall be tested in accordance with the method given in the relevant Annex of ISO *25841 (1).* The thickness of a female condom is unique to each design. The manufacturer shall specify a nominal thickness of the female condom at each of the measurement locations specified in the relevant Annex of ISO 25841

	(*1).* The thickness shall be consistent with the thickness of the female condoms used in the clinical investigation described in Section 1.3. The tolerance shall be ±0.01 mm. For female condoms made from natural rubber latex with sheath thicknesses greater than 0.100 mm a tolerance of ±0.015 mm shall apply.
Quantity of lubricant including powder	
Testing	Samples from each lot shall be tested in accordance with the method given in Section 7.7. The design of a female condom may include lubrication in any of the following forms: 1. lubricant pre-applied directly to the female condom during packaging; 2. lubricant supplied in a separate container to be applied to the female condom by the user; and 3. lubricant both pre-applied to the female condom and supplied in a separate container. The type and amount of lubricant is unique to each female condom design. The manufacturer shall specify the amount of lubricant, which shall be the same as that used in the clinical investigation.
Requirements	The manufacturer shall specify the amount of lubricant, which shall be the mean amount of lubricant used in the clinical investigation. All female condoms in the sample tested shall be within ±15% of the specified mean. Manufacturers shall specify test methods as appropriate to verify the design and to ensure the quality and consistency of the lubricant. The specification for the lubricant should include viscosity. If the lubricant is supplied separately from the female condom, then manufacturers shall provide full details on how the lubricant should be used. These details shall be consistent with the instruction given with the clinical investigation samples. The quantity of lubricant supplied in the container shall be not less than the amount supplied with the clinical investigation samples. The containers for the lubricant shall not leak. An inspection level of S-3 and an AQL of 1.5 are recommended for assessing lubricant container integrity. Consult the purchase order and specification to determine if additional packaging requirements apply to the lubricant container.
Retention features and other additional components	
Sampling	A sample of 13 female condoms shall be tested from each lot.
Testing	The dimensions of all retention features and any other ancillary components, such as insertion features, shall be measured using the methods specified by the manufacturers. Manufacturers are required to specify mechanical properties for the retention features that are relevant to the correct function of the feature. Examples could include stiffness and elastic memory parameters for rings, resilience and recovery times for foams and adhesion properties for adhesive

	pads. The specification requirements shall be based on the lot(s) used in the clinical investigation. Periodically, purchasers and other interested parties may assess the physical properties specified for the internal and external retention devices.
Requirements	The dimensions of the retention features and other ancillary components for every condom tested shall comply with those specified by the manufacturer. The specified dimensions for retention features shall be the same as those for the clinical investigation samples within a tolerance of ±5%. The mean mechanical properties of the retention features shall be the same as those used for the clinical investigation samples within a tolerance of ±10%. All samples tested shall comply.
Individual container markings	
Sampling	A sample of 13 individual containers and, if appropriate, 13 consumer packs shall be taken from each lot.
Testing	The individual packages are visually inspected to verify the required aspects of package marking.
Requirements	The colour, print design and identification markings, including Pantone references and font sizes, shall be as specified by the buyer and annexed to the specification for the product. All samples shall comply.
Verified by visual inspection	The individual containers shall not adversely affect the properties of the female condom. The individual containers shall be sealed and shall provide an adequate level of protection consistent with the materials used to manufacture the condom. The individual containers shall not allow lubricant to leak. The recommended individual containers shall have sufficient mechanical strength to protect the condoms during shipping and storage.
Verified by supplier's data or independent test requirement	The lot numbers on packages should be printed at the time of packaging. If this is not feasible, then manufacturers shall ensure that there are adequate procedures to ensure that the correct lot number is placed on the packages. The individual containers shall have the following markings, which shall be clearly legible under normal and corrected vision: • the identity of the manufacturer or distributor or, if permitted by local regulations, the registered brand or trademark; • the lot number or lot identification code (printed at the time of packaging, not pre-printed); • expiry date – month and year labelled expiry date in language(s) to be specified by the purchaser (printed at the time of packaging, not pre-printed); the year shall be written as a four-digit number and the month as a two-digit number. • instructions for use that are clearly legible in pictorial form and/or in language(s) to be specified by the purchaser (may be supplied separately if unable to print on the packaging); • the statement relating to the effectiveness of the condom if required by the purchaser (see Table A1 in Annex I "Technical basis for the World Health Organization/United Nations Population Fund female condom generic specification"); and

	• a warning about the risk of allergic reactions to the condom if the condom is made from natural rubber latex. Purchasers may specify the use of Braille for specific information including the expiry date. If a separate lubricant and condom are supplied in the same package, then the expiry date shall be the shorter of the two. The expiry date shall be printed on all packages (i.e. the condom package, the lubricant package and any outer or consumer package). All inspected packages and, if appropriate, consumer packs shall comply with the packaging requirements.

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368 3.4 Packaging requirements for shipment

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370 Inspections or verifications in this section will generally be carried out during prequalification, lot-by-
371 lot pre-shipment compliance testing and periodic inspections.

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373 Information included on all packaging shall be in the language specified by the purchaser.

Table 4. Packaging requirements for shipment	
Consumer packaging [a]	No requirements for consumer packs are included in the WHO/UNFPA female condom generic specification. If required, the full design of the consumer pack should be specified in accordance with the requirements of the programme. If information for the user is to be provided
Information	If information is to be provided with the condom, in accordance with local regulations or programme requirements and/or specified by the purchaser, then the following instructions/information should be considered for inclusion in the inner box or the secondary/consumer carton. The language, which should be appropriate for the intended population, shall be specified by the purchaser: • How to handle the female condom carefully, including removal from the package to avoid damage to the condom by fingernails, jewellery, etc. • How and when to insert the female condom; mention shall be made that the female condom should be inserted into the vagina before any contact occurs between the vagina and the partner's body to assist in the prevention of STIs (sexually transmitted infections) and pregnancy. • A statement instructing the user to stop and check if they feel the female condom slipping into or out of the vagina. • If the lubricant is supplied with the condom but in a separate sachet, then instructions on how to use the lubricant shall be provided along with a description of the lubricant and an expiry date.

Table 4. Packaging requirements for shipment	
	• A statement informing the user about which type of additional lubricant can be used with that specific female condom and how the lubricant should be used. • If the female condom is made with natural rubber latex, a statement instructing the user to avoid using oil-based lubricants, such as petroleum jelly, baby oil, body lotions, massage oils, butter and margarine, as these are deleterious to the integrity of the female condom. • A statement instructing the user to consult a doctor or pharmacist about the compatibility of topical medicines and other topical products that may come into contact with the female condom. • Advice on seeking medical assistance as soon as possible should a female condom fail during use. • Advice to discard the female condom and use a new one from an undamaged package if the individual package is obviously damaged. • Advice on withdrawing the penis soon after ejaculation leaving the female condom in place in the vagina. • Instructions for withdrawal and disposal of the female condom. • A statement that the condom is for single use only and that cleaning and reuse can compromise the integrity of the device. • Explanation of any symbol used on the packaging. • If a symbol for latex is used on the packaging, a statement that the female condom is made of natural rubber latex, which may cause allergic reactions, including anaphylactic shock, if the user is allergic to latex. • The date of issue or the date of latest revision of the instructions for use. • If the product is manufactured to conform to all requirements of this document, the number of this document (i.e. ISO 25841). • For female condoms intended for distribution within the European Union, the CE mark. It is recommended that the following statement relating to the safety and effectiveness of the condom be included: "When correctly used every time you have sex, female condoms reduce the risk of unintended pregnancy, HIV and some other sexually transmitted infections. Use a new condom every time you have sex and follow the instructions carefully."
Inner boxes	The inner boxes shall be packed into plastic bags or other bags with waterproof linings, which will be placed in three-wall cartons made from weather-resistant corrugated fibreboard with a bursting test strength of no less than 1,900 kPa. The inner boxes will be marked in a legible manner to facilitate identification in case of subsequent queries. The following information shall be included in the inner box marking: • A description of contents. • Lot identification number. • Month and year of manufacture (including the words "date of manufacture", "month" and "year") in language(s) to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number.

Table 4. Packaging requirements for shipment	
	• Month and year of expiry (including the words "expiry date", "month" and "year") in language(s) to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number. • Manufacturer's name and registered address. • Number of condoms in the box. • Instructions for storage. *Note*: all markings must be legible. Inner box markings can be specified in accordance with programme requirements.
Interior shipping cartons	The inner boxes shall be packed into plastic bags or other bags with waterproof linings, which will be placed in three-wall cartons made from weather-resistant corrugated fibreboard with a bursting test strength of no less than 1,900 kPa. The carton flaps shall be secured with water-resistant adhesive applied to not less than 75% of the area of contact between the flaps, or with water-resistant tape, 75 mm wide, applied to the full length of the centre seams and extending over the ends by not less than 75 mm. The cartons may be secured by plastic strapping in no less than two positions. Alternatively, wire-bound, cleated plywood or nailed wood boxes are acceptable when lined with a material that provides a waterproof barrier. The barrier material must be sealed at the edges with waterproof tape or adhesive, and there must be no sharp protrusions inside the boxes. In some countries, the three-wall corrugated fibreboard available is not of sufficient strength and rigidity to meet stacking requirements or to resist being cut at the corners when the plastic strapping is applied. In such cases, an inner carton of two-walled corrugated fibreboard shall be inserted into the shipping carton before packing the condoms.
Exterior shipping cartons	The exterior shipping carton, like the inner box, shall be marked with information about the contents in a clearly legible manner. Information should be printed on two adjacent sides. The information shall include: • A description of the contents. • Lot identification number. • Month and year of manufacture (including the words "date of manufacture", "month" and "year") in language(s) to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number. • Month and year of expiry (including the words "expiry date", "month" and "year") in language(s) to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number. • Name and address of the manufacturer and/or supplier. • Number of female condoms contained in the carton. • The consignee details. • Instructions for storage and handling.

Table 4. Packaging requirements for shipment	
Lot traceability	Condom lots presented for inspection and acceptance must be complete and packed in their exterior shipping cartons. Provision should be made during production for sufficient additional condoms from each lot to replace those sampled for acceptance testing. Wherever practicable, lots must be shipped in their entirety and be kept whole during containerization and shipping. The manufacturer should take all reasonable steps to maintain the shipments in discrete lots as far as practicable down the distribution chain. These steps may include the use of very large letters for lot codes, colour coding and the grouping of pallets with the same lot number.

[a] Sometimes called wallet packs.

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Annex 1

Technical basis for the WHO/UNFPA female condom generic specification

1. Background

Although the female condom only became commercially widely available in the 1990s, the concept of an internal sheath that can be inserted into the vagina prior to intercourse to protect against pregnancy and sexually transmitted infections (STIs) is certainly not new. According to legend, Minos, the mythical king of Crete, used a female sheath made from a goat's bladder to protect a woman while he cast off his serpent-bearing semen *(1)*. In 1907, Frank Bruce Graham filed United States patent 899,251 for a bag that could be inserted into the vagina of an animal prior to coitus to collect semen for artificial insemination purposes. The bag is described as being made from a flexible material, such as soft rubber, and having a flexible frame or binding at its open end that rests against the vulva and so prevents the bag from being pushed all the way into the vagina. The patent also describes the bag as having a band of less yielding material at an intermediate position along its length, the band being approximately ovoid in section to retain its shape in situ and prevent the walls of the vagina from collapsing the bag.

The device described by Graham has all of the features considered essential in a modern female condom.

During the United States Food and Drug Administration (FDA) panel meeting on 7 March 1989, which was held to review the classification of the Wisconsin Pharmacal Company female condom, reference was made to a device, the Gee Bee Ring, which was distributed in the 1930s as a female condom *(2)*. Bounds *(3)* reported that female condoms were also available in the United Kingdom of Great Britain and Northern Ireland (United Kingdom): the Capote Blanco in the 1920s and the Capote Anglaise and Ladies Own Sheath in the 1960s. None of these products, however, appear to have been widely used or to have achieved commercial success.

Other early examples of female condoms appear in the patent literature. A United States patent, 3,536,066, filed in 1967 by Ludwig, describes a device consisting essentially of a panty or bikini bottom containing a "cul-de-sac proboscis with bellow like circular folds" in the crotch region of the bikini. The woman wears the device. During intercourse the man pushes the "cul-de-sac proboscis" into the vagina. In this patent, Ludwig essentially described what is known today as the panty or bikini condom.

In 1975, Freimark filed United States patent 4,004,591 for a "contraceptive device to be worn internally by women". The patent describes a tubular member made of a compliant material designed to fit snugly in the vagina and with two flaps extending outwardly at the open end intended to cover the labia majora of the wearer and the adjacent epidermal area. Despite many attempts to develop a commercially viable female condom, it is only in the past 20 years that any degree of success has been achieved.

In the late 1980s, a design for a female condom was developed by Hessel, a Danish physician. The product was widely patented around the world (e.g. United States patents 4,735,621 and 4,976,273). Hessel sold the rights to the product to Chartex Resources Limited, a private British company, which in turn selected Wisconsin Pharmacal Company as the United States of America (United States) licensee for the product. In 1996, Wisconsin Pharmacal changed its name to The Female Health Company, a United States public company. The Female Health Company then purchased Chartex and obtained the worldwide rights to the female condom. The Female Health Company merged with Aspen Park Pharmaceuticals in 2016, forming Veru Healthcare.

The Female Health Company's female condom was first launched in a number of European countries, including Switzerland, France, the United Kingdom, Italy and Austria, in 1992. FDA premarket approval was obtained in 1994, clearing the way for the condom to be sold in the United States. The product has been distributed under a number of names, depending on the market and distribution route. These names include Reality, Femidon, Dominque, Femy, Myfemi, Protectiv' and Care.

In 2003, The Female Health Company began the development of a second-generation female condom with the primary intent of reducing the cost of the product. The new version, known as FC2, is manufactured with synthetic latex using a dipping operation, a process similar to that used in the manufacture of male latex condoms and latex medical gloves. FC2 received European marketing authorization (CE mark) in 2005 and FDA premarket approval in 2009. Following the successful

development of FC2, The Female Health Company has stopped manufacturing the original condom, which is now designated FC1.

FC1 and FC2 effectively opened the market for female condoms. A number of other manufacturers have developed or are in the process of developing new types of female condoms. Examples include:

- The VA w.o.w® (worn of women) Condom Feminine® or L'amour made by Medtech Products Ltd, Chennai, India. This product is often called the Reddy female condom after the name of its designer.
- The Woman's Condom developed by PATH (formerly Program for Appropriate Technology in Health) in the United States and now under manufacturing scale-up in China by Shanghai Dahua Medical Apparatus Co., Ltd.
- The Cupid Female Condom manufactured by Cupid Ltd, Mumbai, India.
- The Phoenurse female condom produced and distributed in China by Condombao Medical Polyurethane Co. Ltd, Shanghai, China.

In addition, there are a number of panty or bikini condoms in limited distribution. These products consist of a panty that is worn by the woman and has a means of attaching a sheath. The panty prevents the sheath from being pushed completely inside the vagina.

A very useful update on new designs of female condoms undergoing clinical evaluation was published in 2012 by Beksinska and others *(4)*.

2. Female condom design

Female condoms are designed to be inserted into the vagina before penetration by a male. In principle, a female condom can be inserted some time before intercourse and this is often seen as one of the potential advantages of the device. It is under the control of the woman and, if previously inserted, does not interfere with sexual intercourse. Depending on the specific design, the device may also provide some protection from STIs to the external genitalia, another potential advantage over male condoms.

There are many possible designs of female condoms, but all of those in current distribution or development have the following features:

- A sheath that lines the vagina. The sheath is made from a polymer and is usually elastic. Common materials include polyurethane (FC1, PATH Woman's Condom and Phoenurse), synthetic rubber latex (FC2) and natural rubber latex (Reddy and Cupid).
- An external component that prevents the condom from being pushed into the vagina during intercourse. This may be a ring (FC1, FC2 and PATH Woman's Condom) or a semi-rigid frame (Reddy and Cupid). The external component may be integral with the sheath, as is common in those devices that use a ring, or may be attached to the sheath, as is commonly the case when a frame is used.
- An internal retention feature that keeps the condom inside the vagina. Commonly used features include elastic rings (FC1, FC2 and Phoenurse) and sponges (Reddy and Cupid). The PATH Woman's Condom is unique in including a number of hydrophilic polyurethane foam pads towards the closed end of the condom that adhere gently to the vaginal wall.
- A means of inserting the condom into the vagina. The internal retention feature may be used for this purpose, particularly in the case of those condoms that have an internal ring, or there may be a separate applicator that can be discarded after insertion. The PATH Woman's Condom is unique in having an insertion device made from polyvinyl alcohol that dissolves once inside the vagina and so releases the condom.

Female condoms are usually pre-lubricated, but some are supplied with a sachet of lubricant to be applied immediately before use. Silicone fluids and water-based lubricants are used. Depending on the materials used to manufacture the condom, it may have greater tolerance to a wider range of personal lubricants than male latex condoms. As with male condoms, the products are distributed in individual packages designed to protect the condom during transit and storage. One or more individual packages may be packed in a consumer pack, particularly in the case of products intended for retail distribution. Some materials used in female condom manufacture, for example polyurethanes and synthetic rubber latex, have excellent oxidation resistance, allowing for a wider choice of film materials for the individual package.

3. Regulatory

Male and female condoms are regulated around the world as medical devices. The precise definition of a medical device varies depending on the regulatory authority but all are based on the same general principle that a medical device is an instrument, apparatus, implement, appliance, etc. used for the treatment, diagnosis, monitoring or alleviation of a disease, injury or other similar condition if the

primary intended purpose of the device is not achieved by chemical, pharmacological, immunological or metabolic means.

There are two dominant regulatory systems for medical devices: the United States scheme operated by the FDA and the European CE mark scheme operated within Europe.

Both are legally binding schemes enforced by federal law in the United States and directives in the European Union. These schemes are often used as the basis for many other national schemes. In fact, many national regulatory bodies will take market authorizations under the FDA and CE mark procedures as evidence that a product has been adequately tested for safety and effectiveness. In the public sector condom distribution system, many agencies require FDA and/or CE mark market authorization for male condoms, and similar requirements apply to female condoms.

The classification of medical devices follows different procedures in the FDA and European schemes but in both systems, the category to which a product is assigned depends on the level of risk associated with that product. Devices that carry high levels of risk because of their mode of action, their method of use, the nature of the condition they are treating, or the level and nature of exposure to the device are subject to more stringent requirements for demonstrating their safety and effectiveness. Under FDA procedures, devices are assessed and classified into three categories based on expert panel reviews. Approximately 1,700 different generic types of medical device have been classified this way. The FDA determined, based originally on a panel review held in 1999, that female condoms are Class III (premarket approval) devices, the most stringent class for medical devices. Under European procedures, devices are classified as Class IIb devices in accordance with the set of rules listed in annex VIII of the Medical Device Regulation (MDR) *(5)*.

Irrespective of classification, female condoms are subject to clinical studies to verify their effectiveness and safety. For well-established devices, such as male latex condoms, compliance with an appropriate national, European or international standard is often accepted by regulatory authorities as evidence of an acceptable level of effectiveness. The FDA, for example, will accept compliance with ISO 4074, the international standard for male latex condoms, and/or ASTM D3492-08, the United States standard for male rubber condoms, as sufficient evidence of a satisfactory clinical performance in a 510(k) premarket notification. Similarly, notified bodies within Europe – the organizations responsible for assessing medical devices – will accept compliance with EN ISO 4074 (the European designation

for the international standard for male latex condoms) as sufficient evidence that the condoms comply with the essential requirements of the MDR. Male latex condoms are therefore considered to be well-established products and clinical trials are no longer required as long as they are equivalent to existing products in terms of design, manufacture and materials.

The FDA specifies that female condoms must be approved through the premarket approval process, which requires the submission of a dossier detailing many aspects of the product, including manufacturing information, non-clinical data, safety data and clinical effectiveness data. When reviewing FC1, the FDA required, as part of the premarket approval process, clinical evidence supporting the contraceptive effectiveness of the product. The pivotal study involved the recruitment of 375 subjects in a prospective, multi-centre, single-arm international trial. More details on this study are given later in this paper. FC2 was granted premarket approval on the basis of, inter alia, a pivotal prospective randomized, crossover clinical trial comparing the failure rates of FC1 and FC2 in which 276 subjects were enrolled.

The FDA and the Obstetrics and Gynaecology Devices Panel, which recommended granting premarket approval, accepted that FC2 was broadly equivalent to FC1 on the basis of non-clinical data and functionality data and therefore agreed that a full contraceptive efficacy study of FC2 was not necessary. The FDA's position on the need for contraceptive efficacy studies for new types of female condoms will therefore depend, to some extent, on the degree of equivalence between the new designs and FC1/FC2.

A number of manufacturers of new designs of female condoms have been able to obtain approval for CE marking of the products within Europe without significant clinical data. The exact basis of these marketing authorizations is not clear but, since there is no harmonized standard within Europe for female condoms, there is an underlying presumption that evidence of satisfactory compliance with the essential requirements of the MDR would require clinical investigations. The MDR has now been fully implemented in Europe but the impact of the change on clinical requirements for female condoms remains to be seen.

4. Standards

International and national standards have been developed for many medical devices. Standards often play a key role in the regulatory process for medical devices. It is common practice for regulatory bodies to insist that products meet local and/or international standards as a condition for regulatory clearance. Within Europe, compliance with a harmonized European standard is one method of demonstrating that a product meets the essential requirements of the MDR, facilitating clearance for CE marking. In the United States, the FDA generally requires that a medical device complies with the appropriate United States (ASTM) and/or international (ISO) standards.

International standards are developed and published by the International Organization for Standardization (ISO). ISO is a network of the national standards institutes of 163 countries. It is based on the principle of one-member body per country. The Central Secretariat of ISO is based in Geneva, Switzerland.

ISO standards are developed by technical committees comprising experts from a wide range of backgrounds, representing manufacturers, vendors, users, consumer groups, testing laboratories, private and public sector bodies, procurement agencies, regulatory bodies, governments, research organizations, etc. The standards are consensus driven, industry wide and voluntary. The approval process consists of a series of international reviews and ballots, with a majority of at least two thirds of participating national member bodies approving the standard.

ISO Technical Committee 157, designated ISO/TC 157 non-systemic contraceptives and STI barrier prophylactics, is responsible for developing standards for barrier contraceptives, including male and female condoms. Working Group 18 of ISO/TC 157 developed the first edition of ISO 25841, which was published in 2011. Further revisions were published in 2014 and 2017, mainly to keep pace with the introduction of new types of female condoms over the period and address certain issues with clinical trial design. An amendment to the standard is being progressed to include guidelines for verifying the effectiveness of the test procedures for assessing freedom from holes and package integrity.

ISO/TC 157 Working Group 20 developed and published *ISO 29943-2:2017*, a standard providing guidance on conducting clinical evaluations of female condoms. This standard was developed in parallel with an equivalent standard for clinical investigations on synthetic male condoms.

ISO standards usually specify requirements and test methods for the specific products concerned. In the case of female condoms, which can be made to a variety of designs and from a wide range of materials, specifying certain performance requirements, such as minimum air inflation limits, are therefore not possible. There are similar issues when specifying certain design requirements, such as dimensions. The approach adopted in ISO 25841 is to rely on a clinical evaluation to establish the acceptability and effectiveness of the device and to specify how the manufacturer should set the specification for the product. The standard specifies the test methods that must be used and the properties that must be specified. More details of these requirements are given later in this paper.

5. Clinical studies on female condoms

As the first female condom to be widely marketed, FC1 was subjected to a significant number of clinical studies, the details of which have been published *(6)* and are referenced later in this document. The same is true of FC2 which has now been used as a control condom in a number of clinical studies.

Further clinical studies were in progress at the time of writing, including contraceptive efficacy studies. The results from two major studies on the PATH Woman's Condom, with FC2 as the control, are expected to be published shortly.

5.1 Contraceptive efficacy

An early, prospective study to determine the contraceptive efficacy of FC1 was conducted in the United Kingdom by Bounds *(3)* in 1992. Based on 106 self-selected women who were included in the analysis, the typical-use 12-month pregnancy rate, estimated using life-table analysis, was 15% (95% CI 3.5% to 26%). For those subjects who used the device consistently, the 12-month life-table method failure rate was reported as 5% (95% CI 0% to 11%). It was originally planned that 200 women would be recruited into the study but recruitment had to be cut short because of administrative difficulties with importing the device into the United Kingdom from the United States. Of the women recruited

into the study, 56% dropped out because they found aspects of intercourse while using the device unsatisfactory. Of the women who dropped out, 33% did so in the first month.

The pivotal study by Farr and others *(6)* on FC1 that was used for the basis of FDA premarket approval was conducted by FHI 360 and the Contraceptive Research and Development (CONRAD) Programme with funding from the United States Agency for International Development. The trial was conducted in nine centres (six in the United States, two in Mexico and one in the Dominican Republic). Eligible participants aged 18–40 years in mutually monogamous relationships used FC1 as their only means of contraception for a period of six months in an open-label, non-comparative trial with follow-up at one, three and six months, during which a pelvic examination was performed, the coital log and product use history were recorded and additional supplies of the product were distributed. At six months, or earlier in the case of discontinuation, a Pap smear and a urine pregnancy test were completed, and subjects were asked to complete an open-ended questionnaire to assess product acceptability. There was a further follow-up two weeks later for a final urine pregnancy test. In total, 377 subjects were enrolled in the study with 328 contributing to the final analysis for contraceptive efficacy.

The six-month life-table probabilities of pregnancy in typical use were 12.4% (SE 2.6%) for the United States subgroup and 22.2% (SE 5.3%) for the Latin American subgroup. Over the whole group, the six-month life-table pregnancy rate was 15.1% (SE 2.3%). The difference between the two subgroups was not statistically significant (significance level of 0.05 using a two-sided z-test for life-table probabilities). According to Trussell and others *(7)*, "typical use" means that the female condom was not always used correctly or with every act of intercourse. Comparative rates for the subjects who reported using the condom correctly and with every act of intercourse (perfect use leading to the lowest expected pregnancy rate) were 2.6% (SE 2.7%) for the United States subgroup, 9.5% (SE 6.7%) for the Latin American subgroup and 4.3% (SE 1.8%) over the total group.

Six-month life-table discontinuation rates in the efficacy population were 34.5% (SE 3.2%) for the United States subgroup and 56.2% (SE 4.5%) for the Latin American subgroup. The main reasons for discontinuation in the efficacy population were personal reasons (22.3% of the total group) and accidental pregnancy (11.9% of the total group). Personal reasons included the subject relocating, dislike of the device and loss of partner. Although these discontinuation rates appear high, they are

not dissimilar to the rates recorded in other studies on female barrier methods of contraception, including the sponge (46.4%), diaphragm (43.7–48.5%) and cervical cap (46.9%).

By convention, it is usual to cite 12-month contraceptive failure rates in published studies rather than six-month rates as in this study. Given the high discontinuation rates usually seen in studies on barrier contraceptive methods, recruiting sufficient numbers to provide 12-month data is difficult and very costly. Trussell estimated the 12-month pregnancy rates for the United States subgroup in the study by using comparative data from efficacy studies on other female barrier methods, including the sponge, diaphragm and cervical cap, to estimate the ratio of pregnancy rates in the first and second six-month periods. He concluded that, for the United States subgroup, the 12-month typical-use pregnancy rate should be in the order of 21.1% (cf. 12.4% for the six-month rate) and the perfect-use 12-month rate should be approximately 5.1% (cf. 2.6% for the six-month rate).

Typical comparative 12-month pregnancy rates for other barrier contraceptive methods are given in Table A.1.

Table A.1. Comparative 12-month pregnancy rates for barrier contraceptive methods *(8)*

Method	**% of women experiencing an unintended pregnancy within the first year of use**		**% of women continuing use at one year**
	Typical use	**Perfect use**	
No method	85	85	–
Spermicide	29	18	42
Sponge (parous)	32	20	46
Sponge (nulliparous)	16	9	57
Diaphragm	16	6	57
FC1	21	5	49
Male condom	15	2	53

In a smaller study *(9)* conducted in 10 centres in Japan in which 195 subjects were involved, of whom 190 contributed data on contraceptive efficacy, the six-month life-table pregnancy rate was 3.2% (95% CI 0.7% to 5.7%) for typical use and 0.8% (95% CI 0.0% to 2.3%) for perfect use. The author speculated that the much-reduced pregnancy rate in this study might be due to the lower frequency of intercourse (coital rates were 59% lower than in the United States study reported above).

5.2 Sexually transmitted infection reduction

A number of studies have investigated the role of FC1 in STI-reduction strategies. Some of these have focused on the acceptability of long-term use of the device, for example, Macaluso and others *(10)* and Musaba and others *(11)*, and have not looked at the effectiveness of the device in preventing infection transmission. Even in those studies in which an assessment of the device in preventing infection transmission has been undertaken, it is often not possible to make a reliable estimate of the reduction in STI transmission compared with either the male condom or unprotected intercourse because of study design or study size. In a number of studies, trends in reduced STIs were seen when the female condom was introduced, but in no case in the studies summarized below was statistical significance at the 95% level achieved. In a review of published papers on the female condom, Vijayakumar and others *(12)* concluded that there is limited but convincing evidence that FC1 is effective in increasing protected sex and decreasing STI incidence among women. The review included 137 articles and abstracts related to various aspects of the female condom and a closer analysis of five randomized controlled trials on effectiveness. It should be noted that, because of the ethical issues associated with the exposure of control groups to risk of infection, questionable compliance of study participants and the reliance on self-reporting of condom usage, determining the efficacy of any type of condom against STIs is difficult and the results are often open to challenge.

Macaluso and others (unpublished results in Final Report NIH Contract N01-HD-1-3135) showed that the rate of reinfection in a group of 920 women attending public STI clinics over a period of six months was reduced by 70% (relative rate 0.3, 95% CI 0.1 to 0.6) when they used either male or female condoms consistently and correctly, compared with inconsistent users. STI incidence was lower among consistent users who mixed condom types than among exclusive male condom users. The authors concluded that consistent condom use reduces STI risk, but incorrect use and condom failure may greatly reduce effectiveness. They also concluded that the female condom appears to be at least as effective as the male condom as a barrier to STIs, but it is not possible to determine the relative effectiveness of male and female condoms from this study.

French and others *(13)* followed 1,442 women attending an STI clinic who were randomly assigned to receive either female or male condoms. During follow-up, the women were tested for gonorrhoea, chlamydia, early syphilis and trichomoniasis. The incidence rates for the first new post-intervention STI per 100 women-months of observation were 6.8 in the female condom group and 8.5 in the male

762 condom group (rate ratio 0.79, 95% CI 0.59 to 1.06). The authors concluded that women counselled
763 on, and provided with, female condoms fared no worse than and experienced a non-significant
764 reduction in STIs compared with the male condom group. A potential confounding factor in the study
765 was that women in the female condom arm had continued access to male condoms from sources
766 outside the clinic, with male condoms accounting for one third of condom-protected sex acts in this
767 study arm. Women in the male condom arm had little access to female condoms and therefore rarely
768 used them.
769
770 Soper and others *(14)* compared the rates of reinfection with trichomoniasis after 45 days in a group
771 of women who had received treatment for the disease. The women were assigned to use the female
772 condom in a control group on the basis of their response to a demonstration of the product. Of 104
773 women completing the study satisfactorily, 50 were in the control group and 54 were in the female
774 condom user group, but, of the 54 in the user group, only 20 reported using the female condom
775 consistently. Reinfection rates were 7/50 (14%) in the control group, 5/34 (14.7%) in the non-
776 compliant female condom user group and 0/20 (0%) in the consistent female condom user group.
777 Although there were no infections in the consistent user group, the reduction was not statistically
778 significant compared with the control group ($p = 0.08$) or the non-compliant group ($p = 0.09$). This
779 study suggests that using the female condom consistently reduces the risk of trichomoniasis infection
780 but it was too small, and therefore underpowered, to demonstrate that the reduction was statistically
781 significant.
782
783 Hoke and others *(15)* followed 1,000 sex workers in Madagascar for 18 months to assess whether or
784 not distributing both female and male condoms led to increased protection levels and decreased STIs.
785 For the first six months, participants had access to male condoms only whereas, for the final 12
786 months, they had access to both male and female condoms. The researchers interviewed participants
787 about condom use every two months and tested for chlamydia, gonorrhoea and trichomoniasis every
788 six months. For the six months of male condom distribution only, participants used protection in 78%
789 of sex acts with clients. Following female condom introduction, protection at months 12 and 18 rose
790 to 83% and 88%, respectively. Aggregate STI prevalence declined from 52% at baseline to 50% at
791 month six. With the female condom added, STI prevalence dropped to 41% and 40% at months 12 and
792 18, respectively. The authors concluded that female condom introduction was associated with
793 increased use of protection to levels that reduce STI risk.
794

Fontanet and others (16) estimated that additional protection against STIs would be offered to sex workers in Thailand by giving them the option of using the female condom when clients refused to use a male condom. The women were assigned to two groups, one in which they were instructed to use male condoms consistently (male condom group) and the other in which they had the option of using the female condom if clients refused or were not able to use male condoms (male/female condom group). Establishments, rather than individuals, were assigned to groups to prevent women in the male condom group having access to female condoms. The proportion of unprotected sexual acts (defined as sexual acts in which condoms were not used, were torn, or slipped in or out) and incidence rates of gonorrhoea, chlamydia, trichomoniasis and genital ulcer disease were measured over a 24-week period and compared between the two study groups. Condom use was very high in both groups (97.9% of all sexual acts in the male condom group and 97.3% of all sexual acts in the male/female condom group, $p > 0.05$). Male condom use was lower in the male/female condom group than in the male condom group (88.2% and 97.5%, respectively, $p < 0.001$) but this was counterbalanced by the use of female condoms in 12.0% of all sexual acts in the male/female condom group, contributing to a 17% reduction in the proportion of unprotected sexual acts in this group when compared with the male condom group (5.9% versus 7.1%, respectively, $p = 0.16$). There was also a 24% reduction in the weighted geometric mean incidence rate of STIs in the sex establishments of the male/female condom group compared with the male condom group (2.81 versus 3.69 per 100 person-weeks, $p = 0.18$). These are promising trends but the reductions in the proportion of unprotected sex acts and STIs in the male/female condom group were not statistically significant.

Feldblum and others *(17)* assessed the impact on STI prevalence of a female condom introduction and risk-reduction programme at Kenyan agricultural sites in a cluster-randomized trial to determine whether or not a replicable, community-level intervention would reduce STI prevalence. Six matched intervention sites received an information/motivation programme with free distribution of female and male condoms and six control sites received only male condoms and related information. Participants were tested for cervical gonorrhoea, chlamydia and vaginal trichomoniasis at baseline and then at six and 12 months. Consistent male condom use was more than 20% at 12 months in both arms. Consistent female condom use was reported by 11% and 7% of intervention site women at six and 12 months, respectively. Unadjusted prevalence was 16.5% and 17.4% at the intervention and control sites, respectively, at six months, and 18.3% and 18.5% at 12 months. Logistic regression models confirmed the null effect of the female condom intervention. The investigators concluded that the female condom introduction did not enhance STI prevention at these sites.

5.3 Functionality studies

Given the problems and very high costs associated with conducting contraceptive efficacy studies on condoms, it is common to rely on functionality studies of failure rates including slippage and breakage when assessing the effectiveness of condoms. The rationale behind these studies is that if a condom is made out of a barrier material that does not allow the passage of sperm or the microorganisms that are responsible for STIs, if the condom completely covers the penis or lines the vagina and, if during use the condom does not break or slip off, it should be effective both as a contraceptive and for STI prophylaxis. Functionality studies are generally simpler and much less expensive to run than contraceptive and STI studies and often raise fewer ethical issues. FC2 received FDA premarket clearance on the basis of a pivotal clinical study demonstrating that failure rates were non-inferior to those of FC1, rather than on the basis of a contraceptive efficacy study.

As the number of completed functionality studies on female condoms has increased, there has been a convergence of opinion on the major failure modes associated with these devices. ISO/TC 157 Working Group 18 and the WHO Female Condom Technical Review Committee have reviewed the failure mode definitions. The agreed definitions were published by Beksinska and others *(18)*. They are summarized below:

- 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 is defined as breakage during intercourse or during withdrawal of the female condom from the vagina. Clinical breakage is breakage with potential adverse clinical consequences. The clinical breakage rate is calculated by dividing the number of female condoms reported to have broken during intercourse or during withdrawal by the number of female condoms used during intercourse.
- Total breakage is defined as the sum of all female condom breakages at any time before, during or after intercourse. It includes both clinical breakages and non-clinical breakages. 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 an instance when a female condom slips completely out of the vagina during intercourse. The slippage rate is calculated by dividing the number of female condoms that slipped 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.
- Invagination is defined as an instance when the external retention feature of the female condom is partially or fully 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.

As part of the risk assessment, manufacturers should determine if, because of the design, materials of construction or method of manufacture, any additional failure modes may apply to the specific female condom under consideration.

In a six-month prospective functionality study in which 869 women attended two STI clinics in Alabama, United States, Valappil and others *(19)* compared the failure rates of FC1 and male condoms. The brand of male condom used was not specified in the paper, and it is not stated clearly if a single brand or multiple brands were used. Based on a total of 20,148 acts of intercourse, the breakage rate of female condoms was determined to be 0.1% (95% CI 0.05% to 0.21%), compared with 3.1% (95% CI 2.8% to 3.4%) for male condoms. Slippage rates were determined as 5.6% (95% CI 5.1% to 6.1%) for FC1 and 1.1% (95% CI 0.9% to 1.3%) for male condoms. The definitions of slippage used in this study differ from those specified for male condoms by Steiner and others *(35)* and for female condoms by Beksinska and others *(18)*. The male condom slippage definition did not differentiate between complete slippage off the penis (which is classified as a clinically significant failure since it could lead to pregnancy) and partial slippage (which is not classed as a clinically significant failure). The definition of female condom slippage included both the condom slipping out of the vagina and the condom being pushed into the vagina. The latter failure mode is now classified separately as invagination. No mention was made of the rates of misdirection (i.e. the penis being inserted to the side of the female condom in direct contact with the vaginal wall).

The pivotal clinical study that was used to support the FDA premarket approval review was conducted by Beksinska and others *(20)* in South Africa. It was a multi-centre, randomized, prospective, crossover study comparing the failure rates of FC1 and FC2. A total of 276 women were enrolled with 201 completing the study (73%). All the women were using hormonal contraceptives or an intrauterine device or were sterilized (tubal ligation). The study included women recruited from both urban and rural areas with a wide range of backgrounds, including commercial sex workers, students and attendees at family planning and STI clinics. Participants reported condom failure rates through coital logs and follow-up visits. Vulval inspection and macroscopic examination of the vaginal epithelium were conducted at each follow-up visit. In total, 1,920 FC1 and 1,881 FC2 condoms were used.

Clinical breakage rates during intercourse were 0.47% for FC1 and 0.43% for FC2 (95% CI for the difference –0.62% to 0.53%). Misdirection was 1.26% for FC1 and 0.64% for FC2 (95% CI for the difference –1.33% to 0.09%). Invagination (outer ring pushed completely or partially into the vagina) was 3.14% for FC1 and 2.98% for FC2 (95% CI for the difference –1.24% to 0.91%). Complete slippage of the condom out of the vagina was low, at 0.21% for FC1 and 0.11% for FC2 (95% CI for the difference – 0.39% to 0.19%). Overall, the total clinical failure rate was 5.24% for FC1 and 4.3% for FC2. The upper 95% limit for the difference in total clinical failure rates between FC2 and FC1 was approximately 1%. On the basis of these results, the FDA concluded that FC2 was non-inferior to FC1 with respect to failure rates.

A comparison of three newer types of female condoms, the PATH Woman's Condom, the VA w.o.w Condom Feminine and the Cupid female condom, with FC2 was published by Beksinska and others in 2013 *(21)*. This study confirmed that the three condoms evaluated were within the range specified in ISO 25841 for non-inferiority relative to FC2. More recently, in 2015, two more female condom designs, Velvet (HLL Lifecare Ltd., Thiruvananthapuram, India) and Cupid2 (Cupid Ltd., Mumbai, India), were evaluated against FC2 and again shown to be non-inferior *(21)*.

5.4 Prostate-specific antigen

Functionality studies rely very heavily on self-reporting of condom failures and the assumption that semen does not leak into the vagina unless one or more of the defined types of failures occurs. Self-reporting of failures is not necessarily reliable for a number of reasons, including poor recording and recall of events by the subjects and failure to even notice that the condom has failed. There have been

some instances in studies on male condoms in which reportedly failed condoms have been found to be intact when examined post coitally in the laboratory. For this reason, researchers have investigated other biological markers that can be used to indicate the entry of semen into the vagina. Of these markers, the most widely researched is prostate-specific antigen (PSA), a glycoprotein produced by cells of the prostate gland. At the time of writing, the results of a major study comparing failure mode rates with PSA exposure rates were expected to be published shortly.

PSA is a protease that is present in the seminal fluid at high concentrations, its function being to break down the high molecular weight protein responsible for the seminal coagulum into smaller polypeptides, resulting in liquefaction of the coagulum *(23)*. Because serum PSA levels can be elevated in men with prostate cancer, as well as with some benign prostate conditions, measuring serum PSA levels has become a standard screening test, both for detecting prostate cancer and for monitoring men with the disease. For this reason, a number of quantitative and semi-quantitative assays have been developed for PSA. The availability of routine, validated assays and the high concentrations of PSA found in semen make it an excellent marker for detecting leakage into the vagina in barrier contraceptive studies.

Hobbs and others *(24)* evaluated a rapid PSA test against a quantitative assay to identify semen in vaginal swab specimens taken from 492 women participating in two separate research studies in Bangladesh and Zimbabwe. They found that the rapid test (ABAcard® p30 from Abacus Diagnostics) was 100% sensitive (95% CI 98% to 100%) and 96% specific (95% CI 93% to 97%) compared with the quantitative assay (IMx from Abbott Laboratories) in detecting > 1.0 ng/mL PSA vaginal swab eluate. The rapid PSA results were semi-quantitative and correlated well with PSA concentrations.

Since the late 1990s, a number of researchers have published papers on the use of PSA assays on post-coital vaginal swabs to monitor leakage of semen in studies on both male and female condoms. Lawson and others *(25)* compared three potential semen biomarkers, acid phosphatase activity, PSA and the human seminal plasma antigen (MHS-5), by vaginal swabbing after women were inoculated intravaginally with six measured, increasingly larger doses of their partners' semen. Pre-inoculation levels for PSA were low (0.00–1.25 ng/mL), levels for acid phosphatase were variable (0–350 U/L), and levels for MHS-5 were all negative. All post-inoculation samples were positive for PSA whereas, for acid phosphatase, 64 out of 117 (55%) were positive and 14 out of 120 (12%) were positive. The

authors concluded that PSA immunoassay was the best semen biomarker under the sampling and testing conditions used.

Macaluso and others *(26)* reported a study in which 40 women were exposed to different volumes of their partners' semen (10 µl, 100 µl and 1 mL). Vaginal fluid samples were taken before and immediately after exposure, and then after 1, 24 and 48 hours. PSA was measured using an enzyme-linked immunoassay. Average PSA levels pre-exposure ranged between 0.43 and 0.88 ng/mL. Immediately after exposure, average PSA levels were 193 ng/mL when exposed to 10 µl of semen, 472 ng/mL when exposed to 100 µl of semen and 19,098 ng/mL when exposed to 1 mL semen. The PSA levels declined within one hour and returned to the pre-exposure level at 48 hours. Bahamondes and others *(27)* also showed increasing vaginal PSA detection rates with increasing exposure to semen. They reported that PSA levels were lower for nurse-collected samples than for self-collected samples and attributed this to the delay in sampling associated with nurse collection.

In studies on male condoms, Walsh and others *(28)* compared pre-coital and post-coital vaginal PSA levels after unprotected intercourse and intercourse with intact condoms and deliberately punctured condoms. PSA was detected in 100% (24/24) of vaginal samples collected immediately after unprotected intercourse and in none of the vaginal samples collected more than 24 hours after intercourse (0/90). Excluding uses where the condom failed during intercourse, PSA was detected in 2% (1/47) of the post-coital vaginal samples collected after use of intact condoms and in 41% (14/34) of the samples collected after use of punctured condoms (1 mm holes).

In a further study by Walsh and others *(29)*, 830 couples enrolled in a condom-efficacy study were asked to collect a baseline sample of ejaculate from the inside of the first condom they used and a post-coital vaginal sample whenever a study condom broke or slipped off during intercourse. For those couples (68) who subsequently experienced a condom failure, the PSA levels inside the first condom used averaged 13.4 µg per swab, compared with post-coital vaginal levels after condom breakage of 5.7 µg per swab (data from 79 couples). For those couples experiencing condom slippage off the penis, the average post-coital vaginal PSA level was 2.5 µg per swab (data from 17 couples). These results suggest that, even when a condom fails, there is still some degree of protection.

Several studies on female condoms in which PSA levels have been monitored, usually in addition to the failure modes reported above, have been undertaken. Macaluso and others (30) assessed the

frequency of female condom failure in women recruited in Birmingham, Alabama, by monitoring pre- and post-coital PSA levels in vaginal fluid. A total of 175 women used 2,232 female condoms (FC1). Semen exposure was assessed using two different criteria based on the differences between pre- and post-coital PSA levels. One criterion was more sensitive to semen exposure than the other but more likely to be affected by false positives. The second criterion was less sensitive to false positives but might miss exposure to small quantities of semen. Semen exposure was detected in 7–21 per cent of cases of condom use depending on which exposure criterion was used. Higher rates of exposure were reported when condoms broke (67–73%), slipped in (invagination – 55–74%), leaked (44–57%) or were bypassed (misdirection – 52–57%). Based on logistic regression analyses for repeated measurements, user-reported problems accounted for fewer than 59% of the instances of semen exposure.

The authors concluded that exposure was associated with user-reported problems but that it also occurred in their absence. Reported problems and semen exposure decreased with user experience. The failure rates of male and female condoms were compared in two randomized trials, one in the United States and the other in Brazil (31). In both trials, self-reporting of failures by questionnaire and monitoring of pre- and post-coital vaginal PSA levels were used to assess failure rates. Failure rates by self-reporting were significantly higher in the United States study than in the Brazil study for both female and male condoms. The total percentages of reported problems for female condoms were 29% in the United States and 5% in Brazil. Equivalent results for male condoms were 8% in the United States and 3% in Brazil.

An assessment of the PSA data was done by stratification into four categories: non-exposed (≤ 1 ng/mL), low (> 1 ng/mL to < 22 ng/mL), moderate (22–99 ng/mL) and high (≥ 100 ng/mL). Based on the distribution of PSA levels, it was concluded that there were no statistically significant differences between semen exposure levels in the case of male condoms between the United States and Brazil groups. In the case of female condoms, post-coital vaginal PSA levels in the Brazil group were higher than in the United States group, a result that is in marked contrast to the self-reported failure rates. The authors concluded on the basis of these results that self-reporting may be less reliable than using PSA levels to assess condom failure. Other studies, for example Minnis and others *(32)*, have reported similar conclusions.

Galvão and others (33) reported that semen exposure (post-coital vaginal PSA level of > 1 ng/mL) in the Brazil study occurred more frequently with female condoms (22% of uses) than with male condoms (15%), although the difference was small and not statistically significant at higher PSA levels (≥ 150 ng/mL).

6. Manufacture

Female condoms are made using a number of different manufacturing techniques and generally include additional steps over and above those used in male condom manufacture. The sheath component can be made by welding together pre-formed sheets of material or by dipping. As is the norm for male condoms, the sheath components are subjected to 100% testing to screen out defecting sheaths containing holes or tears than could lead to leakage. Electrical conductivity testing, gas leakage and vacuum retention tests are or have been used. Depending on the design of the condom, it may be necessary to conduct this testing before final assembly of the condom (e.g. insertion of the internal retention feature or mounting the sheath on the external retention frame). Final packing and lubrication follow the same general principles used for male latex condoms but the equipment and procedures may differ.

Given the more complex design of female condoms and the possible need for specialized, automated equipment, the establishment and validation of manufacturing facilities is generally more expensive and demanding than for male latex condoms. Early manufacturing may well be completed on pilot-scale equipment, often with quite a high degree of manual operation. The initial production capacity may therefore be severely limited because of this, and lot (batch) sizes may be unusually small when compared with lot sizes in male latex condom manufacture. These limitations can place particular demands on quality control and quality assurance operations. High levels of testing may be required and statistical controls may need to be introduced to ensure adequate levels of lot-to-lot reproducibility. The selection and characterization of the product for clinical evaluation and other important studies, such as stability testing, can therefore be highly demanding. It is essential that manufacturers can demonstrate that the products selected are typical of normal production and comply with the specification established for the product.

Given that, for many product designs, the initial manufacture will be on a pilot scale, and it is during this period that clinical and other critical evaluations will have been carried out, the subsequent scale-

up of manufacturing operations places special demands on the manufacturers. If, as a consequence of scaling up the manufacturing process, any of the key design or performance properties of the condom change significantly, further clinical and other evaluations may be necessary to confirm that the safety and effectiveness of the product has not been compromised. Manufacturers, auditors and inspectors need to pay special attention to any changes in the scale of manufacture, the type of equipment used or the automation of any of the process steps to ensure that the product is not significantly affected by the changes.

7. Testing

Testing procedures and requirements for female condoms are defined in international standard ISO 25841. Essentially, the test methods for female condoms are derived from those used for male condoms. On a routine lot-by-lot basis, the following key requirements are assessed:

- design;
- dimensions;
- bursting pressure and volume;
- freedom from holes and visible defects; and
- packaging and labelling requirements including pack integrity.

In addition, further testing is required during the design and development phase of the product or following a significant change in the design, materials of construction or manufacturing procedures for the condom:

- barrier properties (lack of permeability to viruses, etc.);
- biocompatibility;
- clinical evaluation, and
- stability/shelf life assessment.

Studies have confirmed that male latex condoms with a minimum thickness of 0.055 mm made using conventional dipping processes have effective barrier properties. Female condoms that have a sheath made from natural rubber latex using conventional dipping processes and with a thickness equal to or greater than 0.055 mm can therefore be assumed to have acceptable viral barrier penetration resistance. These products are therefore exempt from viral barrier testing.

Some regulatory bodies may request more information. For example, the FDA typically requires extensive characterization of the polymeric materials used in the construction of the device, including monomer composition, molecular weights, molecular weight distributions, residual monomer and catalyst composition. The FDA may also request information about the physical properties of the retention features and thermal characterization of the polymeric materials by differential scanning calorimetry. To a significant extent, the nature of the information requested will depend on the materials used. Although this may appear excessive, better characterization of the materials and properties of the condom and its critical components means that any unexpected outcomes from the clinical evaluation will be less likely and implementing essential material and process changes later on will be easier.

Many of the routine tests follow the procedures used for male latex condoms, although some changes in the test equipment may be necessary. For example, new or modified mandrels will probably be required for determining the lengths of the condoms and for conducting the air inflation test. Special mountings with sealing plugs are required for the freedom from holes test. Modifications may also be necessary for the pressure transducers and flow meters in the inflation test equipment to accommodate the differences in bursting pressures and volumes between male and female condoms. Modifications may be necessary for the pack integrity test, given the different dimensions and materials of construction that are used for female condom packs.

Full details of the test methods and equipment are given in the relevant annexes of ISO 25841 and, although this standard has not yet been published, it is unlikely that significant changes will be made to these tests. In addition, manufacturers are required to specify any further information that is needed for testing, such as the dimensions of the mandrels used to measure length and conduct the inflation test. Failure by independent test laboratories to follow the manufacturers' recommendations may result in conflicting or incorrect results.

Specific issues relating to the various test methods are summarized in Sections 7.3–7.8.

7.1 Sampling

The quality of each Lot is estimated by testing a randomly selected sample of condoms from that Lot. The sample sizes are defined in ISO 25841 using sampling plans specified in *ISO 2859–1 Sampling*

Procedures for Inspection by Attributes. These are the most widely used sampling plans for assessing attribute criteria (i.e., whether the product conforms or does not conform to the requirements detailed in the specification).

Sampling for independent testing should be done by either an independent accredited laboratory or by an in-dependent sampling organization and not by the factory producing the condoms. Such sampling is required for prequalification and Pre-shipment compliance testing.

The sampler must verify that each Lot that is sampled complies with the definition of a Lot, as specified in Table 1.

Samples must be:

- taken in accordance with pre-agreed sampling procedures;
- representative of the Lot of condoms;
- randomly selected (preferably based on random numbers);
- taken by or under the personal full-time supervision of the sampler.

The sample, once taken, must be sealed and dispatched under the sampler's supervision.

At the request of the manufacturer or the procurer, a duplicate sample may be taken for use in case of disputes. The sampling agency must issue a report giving full details of the sampling process. The report shall include the sampling procedures, identification of the cases from which samples are taken and the total number of cases offered for sampling. The sampler should mark the cases from which samples are taken for buyer reference at receipt.

An example of an acceptable sampling procedure is the "Square Root + 1" plan, in which the number of cases from which to take samples is determined by calculating the square root of the total number of cases in the lot (i.e. square root of 100 = 10) plus one additional case. The total number of samples required for testing is then randomly selected equally among the cases.

7.2 Acceptance quality limit (AQL)

In ISO 25841 and the *WHO/UNFPA Generic specification*, the limits for the maximum percentage of defective condoms are specified in terms of acceptance quality limits (AQLs). The technical definition of an AQL is given in the glossary in Annex V. In general terms, it is the highest long-term average percentage of defects that is acceptable.

For important performance properties, the AQLs are set as low as practically possible. For example, the limit for freedom from holes is set at 0.25% to ensure that the end user is adequately protected. For properties that are less important and do not affect the performance of the condom, such as non-critical visible defects, slightly higher AQLs are acceptable.

Compliance with the specified AQLs is assessed by testing a sample from each lot. Testing a sample can only give an estimate of the percentage of defective products in a lot. The accuracy of this estimate will increase with the size of the sample. The average percentage of defective products—the process average — can be estimated by pooling the results of testing from many lots. For further details on process average, refer to Annex IV.

As discussed in the previous section, testing is conducted according to sampling plans specified in *ISO 2859–1*. This standard contains sets of tables giving the maximum number of defective products that are allowed in a sample taken from a lot. The sampling plans are designed to give a high probability (usually greater than 95%) of a lot being accepted if the process average of defective products is equal to or less than the AQL. In the long run, therefore, the percentage of Lots being rejected should not exceed 5%. If it does, then there is a risk that the manufacturer is not in compliance with the relevant AQL.

7.3 Freedom from holes testing

Only the water leakage test is specified in ISO 25841. With the possibility of many different designs and materials, the reliability of the electrical conductivity test is questionable. The fill volume for the test is not specified; this will depend to a large extent on the dimensions of the condom and the modulus (stiffness) of the material used for the sheath component. Instead of defining a fill volume, as is the case with male latex condoms, the instruction is to fill the condom with water to the top of

the fill plug. With many materials, this will be satisfactory but there may be issues with condoms made from low-modulus materials. In such cases, the manufacturer will have to specify the fill volume to prevent overfilling of the condom which could lead to excessive stretching and eventual bursting of the condom. For all female condoms, an AQL of 0.25 is specified for freedom from holes, the same requirement as for male condoms.

It has recently been identified that standardized procedures are required to verify the correct operation of the freedom from holes test. An amendment to ISO 25841 was being progressed at the time of writing to include guidance on validation/verification procedures for the test.

7.4 Bursting volume and pressure

The airburst properties of a specific design of female condom are unique to that product and provide an important method of assessing the quality of manufactured incidences. A strict procedure is therefore specified for setting the manufacturer's specification for the minimum bursting volume and pressure for each type of female condom. These limits shall be based on the airburst properties of the lot or lots used in the clinical investigation. The procedure is intended to ensure that all future production is of a quality that is equal to or better than the samples used in the clinical investigation to confirm the effectiveness of the product. If the airburst specification is not based on samples from the actual lot or lots used in the clinical investigation, then the manufacturers shall fully substantiate that the samples used to set the specification are equivalent to those used in the clinical investigation.

Full information regarding the establishment of the specified airburst requirements shall be included in the Product Dossier submitted for review by WHO/ UNFPA. The data submitted shall include the complete set of results used to set the specification.

The following procedure shall be used:

- determine the airburst properties of the lot; or
- determine the lots used in the clinical investigation using a sample size of at least 2,000 female condoms. If more than one lot was used in the clinical investigation, then the sample shall be drawn across all the lots, each individual lot being sampled proportionally to its size; and
- set the minimum airburst limits at 80% of the 1.5 percentile values of the airburst volumes and pressures determined above.

Based on data supplied by manufacturers for both synthetic and natural rubber male latex condoms, an adequate tolerance for the long-term lot-to-lot variability seen in normal manufacture can be achieved by setting the limits at 80% of the 1.5 percentile values.

For the purposes of this generic specification, the relevant percentile x shall be determined by ranking the N data values and taking the value of the n^{th} rank where n = N.x/100 + ½, rounded to the nearest integer (e.g. for N=2,000, the lower 1.5 percentile is the 31^{st} lowest value).

If manufacturers are unable for any reason to test 2,000 female condoms from the lot or lots used in the clinical investigation, then they must provide data to confirm that the condoms used to set the specification and those used in the clinical investigation are equivalent.

Manufacturers need to be aware of the implications of setting the specification in this way. Any future material or manufacturing process change that affects the properties of the condoms such that a revision in the specification is required may invalidate the outcome of the clinical evaluation. Further clinical studies may be required to confirm that the effectiveness of the product has not been compromised. The need for such clinical studies is assessed by conducting a risk assessment in accordance with *ISO 14971*. Regulatory bodies will generally want to review the risk assessment and may or may not accept the conclusions reached by the manufacturer.

7.5 Clinical investigations

A key principle underlying ISO 25841 is that the clinical performance and effectiveness of a condom cannot be determined solely from the design specification and a knowledge of the materials used. It is generally necessary to demonstrate that a new or modified condom design has an acceptable level of clinical effectiveness by conducting a clinical investigation. The type of clinical investigation required depends on how closely the product matches existing female condoms on the market.

If the manufacturer can demonstrate that the new product is sufficiently similar to a design that is already approved and marketed, they may be able to demonstrate that the product has an acceptable level of effectiveness in a functionality study designed to determine the failure rates for each of the possible failure modes identified for the product. If not, the manufacturer may need to complete a full contraceptive efficacy study. To determine the type of trial required, manufacturers are required

to conduct a risk assessment in accordance with *ISO 14971*. A list of the factors to be considered when assessing equivalence with an already marketed product is contained in Table 5. There are no guidelines in ISO 25841 on what constitutes equivalence to a marketed product. This is left to the discretion of the manufacturers and the regulatory bodies that will review any regulatory submission. Manufacturers are strongly advised to undertake discussions with the relevant regulatory bodies and agree on the nature of any clinical investigations that will be required prior to commencing any clinical work.

Table 5. Risk Assessment – Factors to be considered when considering equivalence for assessing clinical evaluation requirements

Design Element	**Property**	**Equivalence Criteria**
Materials	Type	Generic type and subtype (e.g. polyether v. polyester, nitrile v. natural rubber latex)
	Physical properties	Tensile and elongation Tear test
	Barrier Properties	Barrier to bacteriophage Phi X174 according to ISO 25841
Design/dimensions	Shape	Shape - sufficiently similar to achieve equivalent functionality (e.g. line the vagina)
	Length	Greater than or equal to 180 mm: within ±10% Less than 180 mm: within ±5%
	Circumference	Greater than or equal to 150 mm: within +/-10% Less than 150 mm: within ± 5%
	Thickness	Greater than or equal to 0.055 mm: within ±10% Less than 0.055 mm: within ±5%
Retention Features	External	Mode of action Material/properties Shape Dimensions
	Internal	Mode of action Material/properties Shape Dimensions
Insertion Feature		Fitness for purpose and safety
Lubrication	Type	
	Volume	
	Location/Distribution	
Physical properties	Burst volume	
	Burst pressure	
	Freedom from holes	

Ideally, manufacturers should undertake a contraceptive efficacy study to determine the pregnancy rate for the condom. ISO 25841*:2017/AMD 1:2020* specifies that the six-month pregnancy rate should be determined. ISO 25841 and *ISO 29943-2:2017* provide limited guidance on conducting

contraceptive efficacy studies. If such studies are necessary, then it is essential that manufacturers use research organizations and advisers with the appropriate knowledge and expertise to undertake them.

Detailed requirements for the outcome of functionality studies to determine the failure rates are given in ISO 25841 and *ISO 29943-2:2017* for those cases in which the manufacturer can make a sufficiently strong case of equivalence to a marketed product. The marketed product should have a known pregnancy rate determined from a contraceptive efficacy study (or have been evaluated directly against such a product). The upper bound of the one-sided 95% confidence interval for the combined clinical failure rates of the new or modified product shall not exceed that for the control (marketed) product by more than 3%.

7.6 Biocompatibility

Requirements for biocompatibility testing of female condoms are essentially the same as for male condoms. The finished product and its components, together with any lubricant, additive, dressing material or powder applied to it, as well as all retention or insertion devices, must be evaluated. The testing specified in ISO 10993-1, considering the nature and duration of exposure to the product, includes cytotoxicity in accordance with ISO 10993-5 and irritation and sensitization in accordance with ISO 10993-1*0*. Some regulatory bodies may request additional testing, such as subacute and subchronic toxicity in accordance with ISO 10993-11. Accredited laboratories should be used for all biocompatibility testing, and the outcome should be assessed by suitably qualified personnel, such as toxicologists.

7.7 Barrier properties

Because a wide range of materials can be used in the manufacture of female condoms and some of the materials may be placed under permanent stress, such as when stretched over an external frame that forms part of the external retention feature, it is a requirement in ISO 25841*:2017* that the barrier properties of any new or modified design of female condom shall be established by viral penetration studies. The recommended organism is bacteriophage phi X174. Full details of the test method, which was originally developed by the FDA, are given in the draft standard. A titre of bacteriophage (the challenge medium) is placed inside the condom and any leakage through the film is detected by

collecting and culturing a medium placed outside the condom. The use of an appropriate control condom, such as a male condom, meeting the requirement of ISO 4074 is specified.

Interpretation of the test results can be problematic. In most cases, no significant migration of virus across the condom is seen, demonstrating that the condom film is an effective barrier but, with a few individual condoms, it is common to see minor leakage equivalent to a few microlitres of challenge medium. Significant leakage due to the presence of a hole is rarely seen with an individual condom. The low-level leakage, which can be seen with both latex and synthetic materials, is probably due to the presence in some condoms of tiny holes that are too small to be of any clinical significance or to be detected by any of the standard freedom from holes tests. It is for this reason that the use of a control is strongly recommended and care is required when interpreting the results.

With the publication of ISO 25841:2017, however, an exception has been introduced for female condoms that have a sheath made from natural rubber latex using conventional dipping processes and with a thickness equal to or greater than 0.055 mm. The standard states that it can be assumed that such condoms will have acceptable viral barrier penetration resistance and are exempt from testing for conformity with this clause.

7.8 Stability studies and shelf life determination

Manufacturers are required to determine the shelf life of the female condom through real-time studies at (30^{+5}_{-2}) °C. The justification for this temperature range for real-time studies is exactly the same as for male latex condoms; 30 °C is the mean kinetic temperature of the most extreme climatic zones III, IVa and IVb, as classified by WHO *(34)*. The normal temperature tolerance range of ±2 °C has been extended to +5 °C to simplify studies in hot climates where daytime temperatures indoors can exceed 32 °C. Manufacturers electing to use moisture-permeable packing for female condoms should also control the humidity during real-time studies to (75 ± 5)% to meet the requirements for climatic zone IVb.

Pending the outcome of real-time studies, manufacturers may designate a provisional shelf life for a product on the basis of accelerated studies. In recent years, significant progress has been made in simplifying accelerated stability studies of male latex condoms, largely because substantial data have now been generated, allowing the real-time studies at (30^{+5}_{-2}) °C to be correlated with those from

accelerated studies. This has allowed new proposals to be adopted in the WHO/UNFPA specification for male latex condoms whereby specified periods of accelerated ageing at 50 °C can be deemed to be equivalent to specific shelf life periods at (30^{+5}_{-2}) °C.

Following a review of data on the stability of female condoms with sheaths made from natural rubber latex, it has been accepted by ISO/TC 157 Working Group 18 that the above principles relating to male latex condoms can also be applied to these products. ISO 25841*:2017* therefore specifies that, pending the outcome of real-time studies, provisional shelf life claims can be based on the outcome of conditioning the condoms at (50 ± 2) °C for the periods specified below, providing the female condoms conform to the requirements of the standard at the end of the conditioning periods:

- a shelf life of two years after a period of 90 days;
- a shelf life of three years after a period of 120 days;
- a shelf life of five years after a period of 180 days.

There is currently insufficient evidence to adopt the same approach for female condoms made from synthetic materials. ISO 25841 provides guidance on conducting and analysing accelerated studies. The methods of analysis are primarily based on using the Arrhenius relationship which relates changes in the rates of chemical reactions to changes in temperature. There is insufficient data available at present to determine how well these methods work.

7.9 Monitoring quality

As well as reviewing the results of pre-shipment compliance testing on a lot-by-lot basis, it is recommended that purchasers monitor quality on an ongoing basis. This can be done by calculating the process averages or using control charts (e.g. Shewhart charts). Monitoring quality using these methods provides excellent information about trends in product quality and/or early warning of potential problems.

7.10 Testing laboratories

Laboratories may be:

- manufacturers' laboratories;
- independent accredited test laboratories;

- national regulatory laboratories.

Laboratories that test female condoms for regulatory or compliance purposes need to have systems in place to ensure the reliability of their results. ISO has developed a quality management system specifically for laboratories, *ISO 17025*. Laboratories that comply with *ISO 17025* will also operate in accordance with *ISO 9001. ISO 17025* covers the essential elements of *ISO 9001* as well as laboratory-specific requirements, such as technical requirements for equipment, calibration, uncertainty management and technical competence of the staff. The laboratory must conduct regular, traceable calibration of its measuring equipment, have an adequate maintenance system and have systems in place to ensure the technical competence of their staff.

Female condom testing laboratories used for prequalification and pre-shipment compliance testing should be accredited to *ISO 17025*.

There are a number of international mutual recognition agreements among accreditation bodies, which audit each other for quality. The international umbrella body is as follows:

International Laboratory Accreditation Cooperation (ILAC)
The ILAC Secretariat
P.O. Box 7507
Silverwater NSW 2128
Australia
Tel: +61 29736 8222
Fax: +61 2 9745 5311
http://www.ilac.org

It is recommended that all laboratories—national, independent and manufacturers—confirm their competence by participation in condom inter-laboratory proficiency trials. In such trials, laboratories test samples of condoms supplied by the trial organizers. The results of the tests are returned to the organizers who analyze them and provide feedback to each participating laboratory. The test results are reported anonymously to all the test laboratories allowing participants the opportunity to investigate any tests in which their results disagree with those of other participants. Currently, there

may be no opportunity for laboratories to participate in trials specifically using female condoms but the male condom tests are sufficiently similar to be of value.

When assessing a testing laboratory, the following factors should be considered:

- whether the laboratory is accredited by an internationally recognized body;
- whether the laboratory participates in interlaboratory proficiency trials;
- the reputation of the laboratory among large volume purchasers.

7.11 Confirmatory testing

In many countries, national regulatory authorities confine their role to reviewing the data and conclusions reached by the accredited independent laboratory that has been contracted to undertake the pre-shipment compliance testing. In some countries, in contrast, the national regulatory authority may require in-country confirmatory testing. Where feasible, the confirmatory testing should be undertaken by the same laboratory that undertook the pre-shipment compliance testing.

If lot by lot confirmatory testing is required, it should replace, rather than repeat, pre-shipment compliance testing. These requirements should be written into the contractual agreement between the purchaser and the receiving country and/or procuring agency. The testing should be undertaken by a laboratory accredited to *ISO 17025.*

If pre-shipment compliance testing and confirmatory testing are undertaken by different laboratories, there is a risk of contradictory results.

On occasion, the national regulatory authority may have a valid concern regarding possible deterioration of the product during transportation. If this is the case, then confirmatory testing may be undertaken. Local regulatory authorities must take into account the results of pre-shipment compliance testing before reaching any conclusions about the quality of the product.

Confirmatory testing can be restricted to selected lots chosen at random from a shipment or consignment. If one or more of the selected lots fail to comply with the specifications, the remaining lots should be tested. It is recommended that, when such testing is undertaken, priority be given to the critical performance parameters of airburst properties and pack integrity. The risk of statistical lot

failures due to sampling error (i.e. if the sample is not representative of the lot due to chance events) should be considered when interpreting such tests. Occasional differences in results between the pre-shipment compliance tests and the confirmatory tests must be expected.

8. Patents

Given the currently limited availability of female condoms and their relatively recent introduction to the market, there are perhaps a surprising number of published patents covering the product category. Many of these are relatively recent and therefore still in force. Usually, a patent provides a period of protection to the inventor, assignee or licensee for a period of 20 years. A quick search of the international patent literature indicates that the number of patents covering either female condom designs or specific aspects of their manufacture probably runs to several hundred.

The primary purpose of the patent is to provide a period of exclusivity during which the inventor, assignee or licensee is protected from competition by another party copying the specific patented features of the product. Should another party infringe the patent claims by selling a product with the same features that are covered by the patent, the patent holder can bring an action in the civil courts to claim damages for past infringement and obtain an injunction to prevent future sales. In cases of blatant infringement, punitive damages may be awarded in some countries, such as the United States, but usually damages are based on loss of sale and/or licensing fees.

A patent is not a right to practise or use the invention. It is quite possible that a patent holder may still infringe an earlier patent even though the patent they hold is perfectly valid. This is common with patents that cover improvements to products and processes. To ensure that a patent holder can sell a product without fear of infringing an earlier patent, particularly in a crowded patent area, it is essential to conduct a freedom-to-operate review. Such a review considers the claims in prior published patents and determines if there is any risk of infringement. When conducting such a review, it is necessary to be aware of the doctrine of equivalents, which is part of the patent law in many countries. This covers the situation in which minor changes are made so that a product does not fall within the literal claims of an existing patent but nevertheless has essentially the same features or adopts the same solutions. The way in which the rule is applied varies by country but it does mean that making minor changes to a product to avoid an existing patent does not guarantee non-infringement. A professional right to practise review not only reduces the risk of accidentally infringing

an existing prior art patent but also reduces the risk of punitive damages being awarded if there does turn out to be an infringement. In such cases, a manufacturer can claim that they took due care to prevent infringing existing patents.

The cost of a freedom-to-operate review varies significantly depending on the nature of the product and the number of patents that have to be taken into consideration. Given the number of patents in the female condom sector, the cost is likely to be in the order of £5,000 to £15,000 (Pound Sterling).

Finally, it is important to recognize that it is not necessary to patent a new product to develop and sell it. Many designs are simply not patentable over the prior art. To be patentable, a new product or process has to have an inventive aspect that is not obvious to those "skilled in the art" for that particular product or process category. Nor is the possession of a published patent a guarantee that the patent is valid. A published patent can be declared invalid for a number of reasons, one of them being obviousness over existing prior art. The Graham patent from 1907, for example, discloses several features of female condoms that can be found in current designs. This prior art could, in principle, provide grounds for rejecting some claims in modern patents covering these design features.

9. Key issues

There are a number of key issues that need to be addressed when considering the requirements, specification and prequalification of female condoms for public sector distribution. Each type of female condom will be of a unique design, will have its own specification, and will have been subjected to some level of clinical evaluation. In addition, it is necessary to confirm that adequate pre-clinical testing has been conducted to ensure that the product is safe and that adequate manufacturing development and validation have been completed to ensure that the product can be made to a consistent standard. In many cases, the products could be relatively new and therefore manufacturing equipment, processes and procedures may still be undergoing development, scale-up and optimization. Some of the issues that need to be addressed during the review process are summarized below.

9.1. **Pre-clinical testing**. It is essential to confirm that all necessary pre-clinical testing has been carried out to ensure the safety of the product. Unlike with male condoms, consideration has

to be given to any ancillary components of female condoms, such as the retention features and insertion devices. Consideration also has to be given to the extended time period that some female condom designs may be left in the vagina and the wider range of materials that may be used.

9.2. **Product specification.** The manufacturer will have set the specification. It is essential to assess whether the specification is adequate in terms of scope and requirements to ensure that the product is manufactured to a consistent standard. Unlike male condoms, consideration must be given to the adequacy of specification of the ancillary components of female condoms, such as the retention features, insertion devices, lubricant and packaging. Furthermore, it is necessary to confirm that the specification has been correctly based on the characteristics of the products used in the clinical evaluations.

9.3. **Test methods.** Special test equipment will probably be required for each type of female condom, at least as far as mounting mandrels and clamping arrangements for airburst testing and mounts for freedom from holes testing are concerned. Manufacturers will have to supply additional information on test methods and equipment to allow independent laboratories to test the products correctly. Consideration must be given to the need for and desirability of removing ancillary components, in particular the retention features, to facilitate testing.

Specific test methods for the ancillary components may also be required. The number of laboratories appropriately equipped to test female condoms in general, and specific product types in particular, may be restricted. There may be significant restrictions on the number of laboratories for which the scope of *ISO/IEC 17025* accreditation extends to female condoms. Again, it is necessary to consider the ancillary components and determine whether or not test methods are available and adequate to characterize these.

9.4. **Manufacturing and quality management.** As with male condoms, consideration must be given to the quality management system and processes used in the manufacture of the product. With some designs of female condom manufacturing, operations could still be in the transition phase between pilot and full operation. Consideration may have to be given to the equivalence of products manufactured on different scales and possible use of different equipment.

9.5. **Clinical evaluation.** Consideration will have to be given to the types and results of clinical investigations undertaken to confirm the acceptability and effectiveness of the products. As part of this assessment, the equivalence of the design and function of the device compared to marketed products will need to be considered.

9.6. **Shelf life and stability.** Given the wide range of materials that could be used for the construction of female condoms, the number of packaging options and the unique design of each individual product, very limited guidelines can be given on the methods used to justify shelf life claims. The requirements for shelf life verification of ancillary components, such as the retention features, also need to be taken into consideration. Data from real-time studies may be limited given that some products may have only recently been developed or modified.

Data sheets

The manufacturer shall make available to all interested parties a data sheet that contains the following information:

- full details of materials used for the sheath and the retention features;
- specifications for length, width and thickness of the condom and the retention features. The data sheets shall include sufficient information to allow the properties of the condoms and retention features to be assessed by an independent laboratory (e.g. the location of any measurement and any special procedures or equipment that might be required shall be specified);
- the results of air-burst testing of the clinical investigation lot(s). This includes the means and standard deviations for the bursting volume and pressure and the lower limits for bursting volume and pressure as calculated in accordance with the procedures specified in Section 1.4.1 above. Details about the airflow rate, inflation length, mounting equipment and any special preparation procedures required to prepare the condoms for testing shall be provided (including information on whether any of the insertion or retention features need to be removed);
- specifications for amount and type of lubricant and powder used;
- technical drawing(s) showing female condom geometry and correct locations of any retention and insertion features; and

- test methods and specifications for the insertion and retention features.

Data sheets shall be clearly labelled to indicate the date that the original specification was established, the revision number and the date the current revision became effective.

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Appendix I

Summary tables: prequalification and lot-by-lot testing

Tables A.I.1 and A.I.2 summarise the testing methods and requirements for ensuring that there are no packaging defects, general requirements, performance requirements and design requirements for prequalification and lot-by-lot compliance testing. The requirements should be assessed against those specified in the manufacturer's data sheet for the specific product.

Table A.I.1 Summary of prequalification tests (isolated lots)

Characteristics	Sampling	Verification	Requirement
Burst volume and pressure	*ISO 2859-1* Level G-I Minimum Code Letter L (200 samples) For prequalification testing, minimum Code Letter M (315 samples) shall be used	Laboratory testing Comply with manufacturer's specification	Acceptance quality limit (AQL) 1.5
Freedom from holes	*ISO 2859-1* Level G-I For prequalification testing, minimum Code Letter N (500 samples) shall be used	Laboratory testing	AQL 0.25
Visible defects: packages	*ISO 2859-1* For prequalification testing, minimum Code Letter N (500 samples) shall be used	Visual inspection	Critical defects: AQL 0.4 Non-critical defects: AQL 2.5
Visible defects: individual packages	*ISO 2859-1* Level G-I For prequalification testing, minimum Code Letter N (500 samples) shall be used	Visual inspection	Critical defects: AQL 0.4
Design	13 condoms per lot	Visual inspection and measurement	Comply with manufacturer's specification All samples comply
Individual container integrity	ISO 2859-1	Laboratory testing	Laboratory testing AQL 2.5

Table A.I.1 Summary of prequalification tests (isolated lots)			
	Special Inspection Level S-3 For prequalification testing, minimum Code Letter H (50 samples) shall be used		
Colour	13 condoms per lot	Visual inspection	Comply with manufacturer's specification All samples comply
Scents and flavouring	13 condoms per lot	Sensory inspection	Comply with manufacturer's specification
Width	13 condoms per lot	Laboratory testing	All samples comply
Length	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification
Thickness	13 condoms per lot	Laboratory testing	All samples comply
Odour (if necessary)	13 condoms per lot	Sensory inspection	Comply with manufacturer's specification
Inner box	ISO 2859-1 Level S-3	Visual inspection	All samples comply
Exterior shipping cartons	ISO 2859-1 Level S-2	Visual inspection	Comply with manufacturer's specification

Table A.I.2. Summary of lot-by-lot pre-shipment compliance testing and requirements (continuing series of lots)			
Characteristics	**Sampling**	**Verification**	**Requirement**
Burst volume and pressure	*ISO 2859-1* Level G-I	Laboratory testing	AQL 1.5
Freedom from holes	*ISO 2859-1* Level G-I Minimum Code Letter M	Laboratory testing	AQL 0.25
Visible defects	*ISO 2859-1* Level G-I Minimum Code Letter M	Laboratory testing	Critical defects: AQL 0.4 Non-critical defects: AQL 2.5
Visible defects: individual packages	*ISO 2859-1* Level G-I	Visual inspection	Critical defects: AQL 0.4
Individual Container integrity	*ISO 2859-1* Special inspection level S-3	Laboratory testing	AQL 2.5
Design	13 condoms per lot	Visual inspection	Comply with manufacturer's specification All samples comply
Colour	13 condoms per lot	Visual inspection	Comply with manufacturer's specification All samples comply

Table A.I.1 Summary of prequalification tests (isolated lots)			
Scents and flavouring	13 condoms per lot	Sensory inspection	Comply with manufacturer's specification All samples comply
Width	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Length	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Thickness	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Lubricant quantity (including powder)	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Odour (if necessary)	13 condoms per lot	Sensory inspection	Comply with manufacturer's specification All samples comply
Packaging and labelling	13 condoms per lot	Visual inspection	Comply with manufacturer's specification All samples comply
Inner box	*ISO 2859-1* Level S-3	Visual inspection	Comply with manufacturer's specification All samples comply
Exterior shipping cartons	*ISO 2859-1* Level S-2	Visual inspection	Comply with manufacturer's specification All samples comply

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Appendix II

Workmanship and visible defects

1. Introduction

All female condoms in the sample are inspected for workmanship and visible defects as part of the freedom from holes test prior to mounting on the test equipment. The number of condoms exhibiting a visible defect is recorded and defects are classified either according to the type of defect listed below or as specified in the contract.

Visible defects are divided into (a) critical visible defects and (b) non-critical visible defects.

The individual containers in the sample are also inspected for critical visual defects before the samples are removed for testing. Critical visible defects in the packaging that could have an adverse effect on the properties of the condom are listed in Table A.II.1.

2. Types of visible defects in condoms

It is not possible to define all critical and non-critical visible defects, and it may be necessary to exercise some judgement about whether a particular visible defect is critical.

If the visible defect may affect the performance of the female condom, the defect is considered critical. If a defect not listed in Table A.II.1 is considered critical by any party, the purchaser, test laboratory and manufacturer must consult with each other to agree on the classification of the defect concerned.

2.1 Critical visible defects

Critical visible defects may adversely affect the performance of the condom. Condoms with critical visible defects are therefore non-conforming.

ISO 25841 covers the most common critical visible defects. Some of the more common critical visible defects are described in Table A.II.1.

These are evaluated by visual inspection as part of the procedure for freedom from holes testing. An acceptance quality limit (AQL) of 0.4 is applied to these defects.

Other types of critical visual defects are occasionally seen and they should be assessed for their potential effect on the performance and acceptability of the condom. If a defect can be expected to affect the performance, safety or acceptability of the condom, it should be classified as a critical defect.

Table A.II.1 Critical visible defects: AQL of 0.4

Defect	Description
Blister/bubble	An obvious circular or teardrop-shaped thin area with a well-defined border in the film. (Such defects may break under pressure.)
Coagulum (large)	For female condoms made from natural or synthetic rubber latex, rubber particles with any dimension greater than 1 mm. These may cause the condom to fail during use.
Embedded and surface particles	Any particle with any dimension of 1 mm or greater. These particles may be dirt, hair, insects, etc.
Retention features	Broken, cracked, missing, damaged or severely distorted retention features (as in ISO 25841*:2011*). Incomplete attachment of the sheath to the external retaining feature. Disintegrating sponge internal retention features. Presence of sharp edges on retention features that could cause discomfort or damage to the vagina or penis.
Crack marks	For female condoms made from natural or synthetic rubber latex, lines that penetrate the surface of the film, formed by shrinkage of the latex during drying. These do not include flow lines or marks from the mould.
Delamination	For female condoms made from natural or synthetic rubber latex, areas in which the individual layers of latex separate (if the condom is formed by two or more dips in the latex).
Thin areas	Small areas of the condom that are visibly thin. These can show up as bulges with well-defined edges on the freedom from holes test. Condoms that look asymmetrical when filled with water are not necessarily in this category.
Seams	For female condoms made by welding, poorly welded or creased seams that could fail during use or cause discomfort. Large lumps of material within the seam that could potentially cause discomfort or damage to the vaginal mucosa.
Pleat/crease	The film sticks to itself and the pleat/crease cannot be removed by gentle stretching of the adjacent film, and unintentional adhesion to retention features.
General	Any defect that can be seen to adversely affect the performance or safety of the product.

2.2 Non-critical visible defects

Non-critical visible defects are considered minor defects as they may not cause the female condom to fail to meet the specification. Nevertheless, they are undesirable from the user's standpoint. If non-critical visible defects are specified in a purchase specification, an AQL of 2.5 is recommended. Inspection for non-critical visible defects is conducted on the samples used for freedom from holes testing.

Depending on the requirements of the specific user population, the purchaser may wish to include in the specification specific non-critical visible defects, including the most common ones, as listed in Table A.II.2. Detailed descriptions of the non-critical visible defects should be discussed with the manufacturer and included in the contract.

Other types of non-critical defects should be assessed to determine if they will affect the acceptability of the product.

Table A.II.2. Non-critical visible defects: recommended AQL of 2.5

Defect	Description
Small coagula and embedded particles	Small coagula and embedded particles that are not considered to pose any risk of causing the condom to fail during use.
Faulty retention features (minor)	Uneven, partially distorted or otherwise minor defects in the internal and external retention features.

3. Imperfections

Occasionally, imperfections can be seen in female condoms that do not affect the performance or acceptability of the condom. A list of the more common imperfections that fall into this category is given in Table A.II.3. No action should be taken when these imperfections are seen.

Table A.II.3 Imperfections that are not regarded as defects

Phenomenon	Description
Micro-coagula	For female condoms made from natural or synthetic latex, particles of rubber with dimensions less than 1 mm.
Flow lines	Lines of denser material in the film.

Distortion due to rolling at packing	Apparent variations in condom width due to stretching during rolling.
Bulges	Large bulges or distortion of the female condom during the freedom-from-holes test that are due to minor differences in thickness or product design. (These may or may not have well-defined edges.)
Uneven lubricant	A portion of the sheath part of the female condom may appear dry. This can be regarded as an imperfection if it does not interfere with the insertion of the condom into the vagina.
Seam imperfections	Minor creases close to the seams that have no impact on the airburst properties of the condom.
Uneven colour	Minor streaking of the sheath or retention features and uneven colour or discoloration.

Note: Any visible hole anywhere in the female condom, including close to the external retention feature, is not acceptable. These defects are counted as holes if they can be seen before water is added to the condom, even if they are within 25 mm of the open end.

4. Packaging defects

The main packaging defects are listed in Table A.II.4. Additional defects are sometimes detected only after shipment.

4.1. Individual packages

The requirements for individual packages are specified in Table 3 of the WHO/UNFPA female condom generic specification.

4.2. Consumer packs

No requirements for consumer packs are included in the WHO/UNFPA female condom generic specification. Purchasers should fully specify requirements in accordance with condom programme needs. Compliance should be assessed through visual inspection, using a sampling plan in accordance with *ISO 2859-1* Inspection Level S-3. It is recommended that an acceptance quality limit (AQL) of 2.5 be applied for consumer pack requirements.

4.3. Cartons and marking

Purchasers should fully specify requirements in accordance with condom programme needs. Compliance should be assessed through visual inspection, using a sampling plan in accordance with *ISO 2859-1* Inspection Level S-3. It is recommended that an AQL of 4.0 be applied for carton requirements.

Table A.11.4 Packaging defects

Consumer packs	Cartons and markings
Empty or partially empty packs Discolouration Delamination of the packaging film Illegible printing Missing manufacturer's name Incorrect/missing lot number Incorrect/missing date of manufacture Incorrect/missing expiry date	Non-permanent markings Empty cartons or cartons not filled to order Damaged cartons that may affect the integrity or the quality of the condoms inside Number of condoms not as specified Packages or strips not as specified; packaging/packing materials not as specified, missing, damaged or non-serviceable Illegible printing Missing manufacturer's name Incorrect/missing lot number Incorrect/missing date of manufacture Incorrect/missing expiry date Shipping cartons inadequately closed and secured Poor application of internal packaging and packing material; distorted intermediate packages

Appendix III

Guidelines on the assessment of odour and fragrances

Odour and fragrances are best assessed by a panel. There are certain guidelines that apply when assessing the odour and effectiveness of fragrances on condoms. Following these guidelines should help provide a more consistent level of odour assessment. Recommendations include the following:

- The panel should consist of between 6 and 10 individuals.
- Panellists should not wear perfume, smoke or be exposed to a strong odour on assessment days.
- Panellists should be trained and should undergo periodic assessments using appropriate reference odours and samples.
- Odour assessments should not be carried out in a factory or other environments in which a strong background odour may be present.
- Odour assessments should be done blind and in a random order, without the panellists being aware of the source of the samples.
- Adequate time should be allowed between samples for the panellists' olfactory sense to recover.
- To prevent fatigue, the number of samples evaluated in one session should be limited.
- An appropriate grading system should be developed to quantify the intensity, acceptability and type of odour. For example, odour intensity can be rated on a balanced scale from 0 (no perceptible odour) to 6 (extremely strong odour).
- Control samples should be included to allow comparisons to be made between different panels and different sessions.
- The time delay between opening a condom pack and smelling the condom can be critical. This time should be standardized and preferably short.

It is recommended that manufacturers retain unopened samples for reference purposes and to help resolve disputes. Retained samples should be kept for the duration of the shelf life of the product and stored in line with the manufacturer's recommendations.

Appendix IV

Applicable documents

Various external documents form part of the World Health Organization (WHO)/United Nations Population Fund (UNFPA) specification, and the buyer may wish to mention them in any invitation to bid or order sent to the supplier. In every case, the relevant edition of the document is the one in force on the date of the invitation to bid.

These are standards published by the International Organization for Standardization (ISO).

Copies can be obtained from the national standardization organization in the buyer's country or from:
International Organization for Standardization Central Secretariat
Chemin de Blandonnet 8
CP 401-1214 Vernier
Geneva
Switzerland
Telephone: +41 22 749 0111
Email: central@iso.org
Website: http://www.iso.org

Latex condoms

ISO 4074:*2015 Natural rubber latex male condoms – Requirements and test methods*

Female condoms

ISO 25841:*2017/AMD 1:2020 Female condoms – Requirements and test methods*

Testing methods

- ISO 25841:*2017/AMD 1:2020 Female condoms – Requirements and test methods*
- ISO 4074:*2015 Natural rubber latex male condoms – Requirements and test methods*
- *ISO 12243:2003 /AMD 1:2012 Medical gloves made from natural rubber latex – Determination of water-extractable protein using the modified Lowry method*

- *EN 455-3: 2015 Medical gloves for single use - Part 3: Requirements and testing for biological evaluation*
- *ASTM D5712-15(2020) Standard Test Method for Analysis of Aqueous Extractable Protein in Latex, Natural Rubber, and Elastomeric Products Using the Modified Lowry Method*
- *ISO 2859-1:1999 Sampling procedures for inspection by attributes – Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection*
- *ISO 29941:2010 Condoms — Determination of nitrosamines migrating from natural rubber latex condoms*