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Female condoms — Requirements and test methods

Préservatifs féminins — Exigences et méthodes d'essai

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 157, *Non-systemic contraceptives and STI barrier prophylactics*.

This second edition cancels and replaces the first edition (ISO 25841:2011), which has been technically revised.

Introduction

A female condom is a sheath that completely lines the vaginal canal and is designated to be retained in the vagina during sexual intercourse and after withdrawal of the penis to prevent pregnancy and transmission of sexually transmitted infections (STIs).

A female condom is distinguished from a male condom in that it is retained in the vagina after withdrawal of the penis. The external component of the device can provide some coverage to the external female genitalia. Non-porous, intact, polymer films can be effective barriers to human immunodeficiency virus (HIV), to other infectious agents responsible for the transmission of STIs, and to spermatozoa. Female condoms made from polymer films can be effective for contraceptive purposes and in the prevention of STI transmission. To be effective, it is essential that female condoms completely line the vaginal canal, be free from holes and defects, have adequate physical properties so as not to break during use, are correctly packaged to protect them during storage, and are correctly labelled to facilitate their use.

To be safe, it is essential that the female condom and any lubricant, additive, dressing, individual packaging material, or powder applied to it neither contain nor liberate substances in amounts that are toxic, sensitizing, locally irritating, or otherwise harmful under normal conditions of storage or use.

Female condoms are non-sterile medical devices, but manufacturers are advised to take appropriate precautions to minimize microbiological contamination of the product during manufacturing and packaging. To ensure high quality products, it is essential that female condoms be designed and produced under a good quality management system. Reference can be made, for example, to ISO 9000, ISO 9001, ISO 9004, ISO 13485, and ISO 14971. To estimate the shelf-life of any new or modified female condom, manufacturers conduct stability tests before the product is placed on the market. This ensures that manufacturers have adequate data to support shelf-life claims and that these data are available for review by regulatory authorities, test laboratories, and purchasers. They are also intended to limit the need for third parties to conduct long-term stability studies. Real-time shelf-life studies are also initiated, but not necessarily completed, prior to placing the product in the market.

Because female condoms are a relatively new class of devices and designs of female condoms vary considerably, clinical investigations in humans are necessary to continue to build evidence of safety and efficacy. These investigations enable an assessment of the overall performance of internal and external retention features, failure modes, safety, and effectiveness of female condoms. This International Standard represents minimal requirements and test methods and acknowledges that new designs can require further due rigour of retention and other features as well as additional definition of specifications and test methods by the manufacturer.

All these issues are addressed in this International Standard.

Female condoms — Requirements and test methods

1 Scope

This International Standard specifies the minimum requirements and test methods for female condoms, which are supplied to consumers for contraceptive purposes, assisting in the prevention of sexually transmitted infections.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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 4074, *Natural rubber latex male condoms — Requirements and test methods*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-5, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*

ISO 10993-10, *Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization*

ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14155 (all parts), *Clinical investigation of medical devices for human subjects*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 15223 (all parts), *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied*

3 Terms and definitions

For the purposes of this document, the terms and definitions in ISO 2859-1 and the following apply.

3.1
acceptance quality limit
AQL
quality level that is the worst tolerable process average when a continuing series of lots is submitted for acceptance sampling

[SOURCE: ISO 2859-1:1999, 3.1.26]

3.2
consumer package
package intended for distribution to a consumer, containing one or more individual container(s) of female condoms

3.3
date of manufacture
date of formation of the female condom sheath or the date the female condoms are packed in their individual containers provided, in the latter case, a maximum period of bulk storage is specified and shelf-life studies have been conducted on female condoms that have been subjected to the maximum bulk storage period

3.4
expiry date
date at the end of the shelf-life

3.5
female condom
sheath that completely lines the vaginal canal and is designed to be retained in the vagina during sexual intercourse to prevent pregnancy and STIs

3.6
identification number
number, or combination of numerals, symbols, or letters used by a manufacturer on consumer packages to uniquely identify the lot numbers of individual female condoms contained in that package, and from which it is possible to trace those lots through all stages of manufacturing, packaging, and distribution

Note 1 to entry: Whenever the consumer package contains only one kind of female condom, the identification number can be the same as the lot number. However, if the consumer package contains several different types of female condoms, for instance, female condoms of different shapes or colours, the identification number is different from the lot number.

3.7
individual container
primary package containing a single female condom

3.8
inspection level
relationship between lot size and sample size

[SOURCE: ISO 2859-1:1999, 10.1]

3.9
lot
collection of female condoms of the same design, colour, shape, size, and formulation, manufactured at essentially the same time, using the same process, raw materials of the same specifications, common equipment, and packed with the same lubricant and any other additive or dressing in the same type of individual container

Note 1 to entry: This International Standard does not specify the size of a lot; however, it is possible for a purchaser to do so as part of the purchasing contract. Attention is drawn to the difficulties that can be associated with the distribution and control of very large lots. The recommended maximum individual lot size for production is 500 000 female condoms.

3.10
lot number
number or combination of numerals, symbols, or letters used by the manufacturer to identify a lot of individually packaged female condoms, and from which it is possible to trace that lot through all stages of manufacture up to packaging

3.11
lot test
test to assess the conformity of a lot

Note 1 to entry: A lot test can be limited to include only those parameters that can change from lot to lot.

3.12
non-visible hole
hole in a female condom that is not visible under normal or corrected vision, but is detected by a suitable water leak test

Note 1 to entry: Leakage during testing can be detected, for instance, by rolling a female condom on absorbent paper.

Note 2 to entry: Suitable tests are specified in this International Standard.

3.13
sampling plan
specific plan that indicates the number of units of product from each lot which are to be inspected (sample size or series of sample sizes) and the associated criteria for determining the acceptability of the lot (acceptance and rejection numbers)

3.14
shelf-life
time from date of manufacture to the claimed expiry date during which condoms are required to conform to specified requirements

3.15
total clinical failure
sum of female condoms that clinically break or slip, or are associated with misdirection, invagination, or any additional failure mode(s) identified in the risk assessment which results in reduction of the female condom protective function

Note 1 to entry: Total clinical failure rate is calculated by dividing the number of female condoms with a clinical failure by the number of female condoms used during sexual intercourse.

3.16
visible hole
hole or tear in the female condom that is visible under normal or corrected vision

3.17
visible defect
other than a visible hole, broken, missing, or severely distorted retention feature, permanent crease with adhesion of the film, or unintentional adhesion of the film to retention feature, including defect particles from female condoms or other materials embedded in the female condom wall

4 Quality verification

Female condoms are produced in large quantities. Inevitably, there is some variation between individual female condoms. A small proportion of female condoms in each production run might not meet the requirements in this International Standard. Furthermore, the majority of the test methods described in this International Standard is destructive. For these reasons, the only practicable method of assessing conformity with this International Standard is by testing a representative sample from a lot or series of lots. Basic sampling plans are identified in ISO 2859-1. See ISO/TR 8550 for guidance on the selection of an acceptance sampling system, scheme, or plan for the inspection of discrete items in a lot. For testing purposes, sampling shall be conducted by lot number, not by identification number. Handling and storage conditions shall be documented before drawing the samples.

Sampling plans shall be selected to provide an acceptable level of consumer protection. Suitable sampling plans are given in Annexes A and B.

Annex A describes sampling plans, based on ISO 2859-1, and is most applicable to manufacturers or purchasers assessing the conformity of a continuing series of lots. The full level of consumer protection available depends upon the switch to tightened inspection if deterioration in quality is detected. The switching rules cannot offer full protection for the first two lots tested, but become progressively more

effective as the number of lots in a series increases. The sampling plans in Annex A are recommended when five or more lots are being tested.

Annex B describes sampling plans, based on ISO 2859-1, which are recommended for the assessment of isolated lots. It is recommended that these sampling plans be used for the assessment of fewer than five lots, for example in cases of dispute, for referee purposes, for type testing, for qualification purposes, or for short runs of continuing series of lots.

It is necessary to know the lot size in order to derive from ISO 2859-1 the number of female condoms to be tested. The lot size varies among manufacturers and is regarded as part of the process and quality controls used by the manufacturer.

Instead of concentrating solely on evaluation of the final product, the design and manufacture of the female condoms shall conform to the appropriate requirements of ISO 13485, which include the following:

a) controls in the work environment to ensure product safety;

b) focus on risk-management activities and design transfer activities during product development;

c) specific requirements for inspection and traceability for implantable devices;

d) specific requirements for documentation and validation of processes for sterile medical devices;

e) specific requirements for verification of the effectiveness of corrective and preventive actions.

5 Design

5.1 General

Female condoms shall be designed to prevent pregnancy and STIs during vaginal intercourse. A female condom is distinguished from a male condom in that it is retained in the vagina after insertion. A female condom can be made from natural rubber latex (NRL) or synthetic materials.

The design of a new female condom shall take into consideration the following design aspects:

a) product insertion into the vagina;

b) product retention during sexual intercourse or penile removal;

c) penile misdirection during sexual intercourse;

d) safe product removal after sexual intercourse.

5.2 Product insertion feature

Designs for female condoms shall include either a feature or tool to aid in the proper insertion and deployment of the female condom or methods for insertion of the female condom without such additional aids.

The insertion feature design, materials, and/or method shall be evaluated for function as part of design validation and clinical evaluation of the finished female condom device described in Clause 8.

The insertion feature materials shall be evaluated for biocompatibility (irritation, sensitization, cytotoxicity, and acute systemic cytotoxicity) as an integrated feature of the finished female condom device in accordance with Clause 7.

Manufacturers shall identify specifications and test methods as appropriate to verify the design and to ensure the quality and consistency of components and materials used for each insertion feature. Examples of specifications the manufacturer should consider include critical dimensions, durometer, stiffness, and density.

5.3 Retention features

Designs for female condoms shall incorporate intra-vaginal retention features to retain the female condom within the vagina during sexual intercourse and permit safe withdrawal after use. Intra-vaginal retention features can be affixed on or placed within the sheath. Examples of intra-vaginal retention mechanisms include, but are not limited to, elastomeric rings and open or closed cell foam components.

Designs for female condoms shall incorporate external retention features to keep the open end of the female condom open during sexual intercourse, prevent misdirection of penis, and prevent female condom invagination. External retention features include, but are not limited to, annular, triangular, or other-shaped components affixed to the open end of the female condom.

Retention feature designs, materials, and/or methods shall be evaluated for function as part of design validation and clinical evaluation of the finished female condom device described in Clause 8. They shall also be evaluated in this manner to ensure the features stay affixed to the sheath or are retained within the sheath so that they remain intact during sexual intercourse and during product withdrawal, such that the features are completely removed from the vagina when the female condom is removed from the vagina.

Retention feature materials shall be evaluated for biocompatibility (irritation, sensitization, and cytotoxicity) as an integrated feature of the finished female condom device in accordance with Clause 7.

Manufacturers shall identify specifications and test methods as appropriate to verify the design and to ensure the quality and consistency of components and materials used for each retention feature. Examples of specifications the manufacturer should consider include critical dimensions, durometer, stiffness, and density.

5.4 Lubrication

The design of a female condom can include lubrication in any of the following manners:

a) lubricant pre-applied directly on the packaged female condom as supplied;

b) lubricant supplied in a separate container for application to the female condom by the user;

c) both pre-applied and as a separate container.

The type and amount of lubricant is unique to each female condom design. The manufacturer shall specify the range for the mass of lubricant consistent with the mass of lubricant used in the clinical trial described in Clause 8. When tested in accordance with the method given in Annex C, taking 13 female condoms from each lot, no female condom lubricant mass measurement shall be outside of the manufacturer's specified range.

Manufacturers shall identify specifications and test methods as appropriate to verify the design and to ensure the quality and consistency of the lubricant. Examples of specifications the manufacturer should consider include viscosity.

5.5 Dimensions

5.5.1 Length

The length of a female condom is unique to each design. The manufacturer shall specify a nominal value and the range for the length of female condoms consistent with the length of the female condoms used in the clinical trial described in Clause 8. When tested in accordance with the method given in Annex D, taking 13 female condoms from each lot, no female condom length measurement shall be outside of the manufacturer's specified range.

5.5.2 Width

The width of a female condom is unique to each design. The manufacturer shall specify the range for the width of the female condom consistent with the width of the female condoms used in the clinical trial described in Clause 8. When tested in accordance with the method given in Annex E, taking 13 female condoms from each lot, no female condom width measurement shall be outside of the manufacturer's specified range.

5.5.3 Thickness

The thickness of a female condom is unique to each design. The range for the thickness of the female condom shall be specified by the manufacturer, based upon the female condoms that are used in the clinical trials. When tested by the method given in Annex F, taking 13 female condoms from each lot, no female condom thickness measurement shall be outside of the manufacturer's specified range (from the clinical trials).

5.6 Risk assessment

5.6.1 A risk assessment for the product shall be conducted in accordance with ISO 14971. The assessment shall identify all potential failure modes for the device as well as any other safety and efficacy concerns. Failure modes identified in the risk analysis shall be compared to those listed in 5.6.2. In addition to these known failure modes, any new failure modes shall be assessed in the design and execution of any pre-clinical or clinical investigations of the female condom. Manufacturers shall make the results of the risk assessment available to regulatory authorities.

5.6.2 The following are definitions of known female condom failure modes.

a) Clinical breakage is defined as breakage during sexual 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 sexual intercourse or during withdrawal by the number of female condoms used during sexual intercourse.

   NOTE Total breakage is defined as the sum of all female condom breakages at any time before, during, or after sexual 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.

b) Slippage is defined as an instance when a female condom slips completely out of the vagina during sexual intercourse. The slippage rate is calculated by dividing the number of female condoms that slipped by the number of female condoms used during sexual intercourse.

c) 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 sexual intercourse.

d) Invagination is defined as an instance when the external retention feature of the female condom is partially or fully pushed into the vagina during sexual intercourse. The invagination rate is calculated by dividing the number of events of invagination by the number of female condoms used during sexual intercourse.

6 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-X 174. When tested in accordance with the method given in Annex H, viral penetration properties shall be compared with those of a male latex condom that meets the requirements of ISO 4074.

7 Biocompatibility

Biocompatibility for the finished product and its components shall be established. The female condom, together with any lubricant, additive, dressing material, or powder applied to it, shall be tested as well as all retention or insertion devices, whether affixed or removable. Accredited laboratories shall be used for the testing.

Since the female condom is in repeated contact with surface mucosa and possibly compromised tissue surfaces, the testing shall be conducted to demonstrate that the materials are neither cytotoxic nor cause sensitization, mucosal irritation, or acute systemic cytotoxicity in accordance with the relevant clauses of ISO 10993-1, ISO 10993-5, ISO 10993-10, and ISO 10993-11, respectively. If there is a likelihood of systemic absorption of any components or residuals, mutagenicity testing shall be performed.

Regulatory bodies can require that the results be interpreted by a qualified toxicologist. The biological assessment report shall justify that the product is safe under normal conditions of use. All data generated in these evaluations shall be made available to regulatory authorities on request.

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 subject to this International Standard. Suitable material safety data sheets shall be supplied on request for materials used in the manufacture of products conforming with this International Standard.

8 Clinical (human use) investigations

8.1 Clinical investigations of female condoms in humans shall be conducted in accordance with ISO 14155 (all parts), and are intended to be conducted with a future International Standard on functionality studies of acute failure events based on self-reports.

NOTE Clinical investigations can also be subject to local regulatory requirements.

8.2 In order to assess the safety and effectiveness of a new female condom design, a contraceptive effectiveness study shall be conducted. The study design shall be adequate to allow the 6-month pregnancy rate to be computed using life table methods with at least 100 women years of data (e.g. 200 women completing 6 months). The 12-month pregnancy rate can be extrapolated from the 6-month data providing it is made clear that the value obtained is an estimate and the method of extrapolation is documented. The study should also measure all the rates of all failure modes identified in Clause 5.

8.3 New female condom designs that are sufficiently similar to a design that is already approved and marketed can claim exemption from the requirement of 8.2. If a new female condom design and specifications are sufficiently similar to those of a marketed device and that marketed device has a known pregnancy rate established from a clinical effectiveness study, the manufacturer can refer to the estimated pregnancy rate of the marketed device instead of conducting a contraceptive effectiveness study on the new device. If there is no suitable control female condom available in the market with an established pregnancy rate, then the manufacturer can use an alternative female condom that has been evaluated directly against a device with an established pregnancy rate as the control.

To claim exemption from the requirements of 8.2, the following requirements shall be met:

a) The manufacturer shall conduct a risk analysis in accordance with 5.6.

b) The manufacturer shall establish that the new female condom design and specifications are sufficiently similar to those of a marketed female condom, after assessing the impact of each difference in dimension, material, insertion, and retention feature or method, on the incidence of each failure mode described in 5.6.2, on the incidence of new failure modes, and on the efficacy of the female condom in preventing pregnancy and STI transmission. To be considered sufficiently similar to a marketed device, the risk analysis shall demonstrate that the new female condom can be expected to have the same failure modes as the marketed device and no new failure modes or

other risk factors. Manufacturers shall make the results of this assessment available to regulatory authorities.

c) The manufacturer shall conduct a randomized controlled clinical investigation comparing the new female condom to a control female condom and the following.

   1) The control female condom shall meet the bursting volume and pressure, freedom from holes, and visible defects requirements of Clauses 9, 11, and 12, and shall have a known pregnancy rate established from a clinical effectiveness study. If there is no suitable control female condom available in the market with an established pregnancy rate, then the manufacturer can use an alternative female condom that has been evaluated directly against a device with an established pregnancy rate as the control.

   2) The total clinical failure rate of the new female condom shall be shown to be non-inferior to the total clinical failure rate of the control female condom.

   3) The upper bound of the 95 % one-sided confidence interval for the new female condom total clinical failure rate minus the control female condom total clinical failure rate shall be less than or equal to 3 %.

   4) The bound shall be calculated using a method that accounts for the unique characteristics of data such as

      i) each study participant can contribute data from more than one female condom use, and

      ii) possibly low event rates.

   5) The control female condom total clinical failure rates shall not be lower than 1 %.

9 Bursting volume and pressure

9.1 Minimum values

Manufacturers shall establish appropriate minimum pressure and volume limits for the specific female condom based on the airburst properties of the lot or lots used for the clinical trial.

For products in the market prior to the publication of this International Standard, manufacturers shall comply with the procedure in 9.1 or can use existing specifications as established by their regulatory bodies for bursting properties. The specifications shall be consistent with the requirements in 9.1 based on a representative sample of the product tested at the time of the clinical trial. Information regarding the establishment of these values shall be made available to regulatory and governmental authorities upon request.

The following procedure shall be used.

a) Determine the airburst properties of the lot or lots used in the clinical study using a sample size of at least 2 000 female condoms. If more than one lot was used in the clinical study, the sample shall be drawn across all the lots, each individual lot being sampled proportionally to its size.

b) Set the minimum airburst limits at 80 % of the 1,5 percentile values of the airburst volumes and pressures determined above (see 9.1).

NOTE Based on the data supplied by the manufacturers for both synthetic and natural rubber male latex condoms, taking 80 % of the 1,5 percentile values provides an adequate tolerance for the long-term lot-to-lot variability seen in normal manufacture.

For the purposes of this International Standard, the relevant percentile, x, shall be determined by ranking the N data values and taking the value of the n-th rank where $n = Nx/100 + 1/2$ rounded to the nearest integer (e.g. for N = 2 000, the lower 1,5 percentile is the 31st lowest value).

9.2 Sampling and requirements

Whenever tested by the methods given in Annex I, the bursting volumes and bursting pressures shall not be less than the minimum values established by the procedures described in 9.1. The compliance level shall be an AQL of 1,5 for non-conforming female condoms. A non-conforming female condom is defined as a female condom that fails the requirements for volume and/or pressure, or any female condom that exhibits any leakage during airburst testing.

10 Tests for stability and shelf-life

10.1 General

Manufacturers shall verify that the female condoms conform to the airburst, freedom from holes, visible defects, and labelling requirements of Clauses 9, 11, and 12 and 13.1 until the end of the labelled shelf-life. Shelf-life claims shall not exceed 5 years.

Data supporting the shelf-life claims made by the manufacturer shall be made available to the appropriate regulatory authorities and direct purchasers upon request.

Before a new or modified female condom design is placed in the market, the following requirements shall be met.

a) A real-time stability study, as described in 10.2 to determine shelf-life, shall have commenced.

b) Pending completion of the real-time stability study, shelf-life shall be estimated as described in 10.3.

For existing designs on the market at the date of publication of this International Standard, real-time data in a form consistent with Annex K, at a temperature of (30^{+5}_{-2}) °C, shall be acceptable to verify the shelf-life claims.

10.2 Procedure for determining shelf-life by real-time stability studies

After testing in accordance with Annex K, the female condoms shall meet the requirements of Clauses 9, 11, and 12 and 13.1.

If the real-time data indicate a shorter shelf-life than that claimed on the basis of accelerated ageing (see 10.3), the manufacturer shall notify the relevant regulatory authorities and direct purchasers. The manufacturer shall change the shelf-life claim for the product to one based on the real-time stability study. In no case shall shelf-life exceed 5 years. For female condoms placed on the market, real-time stability studies shall be completed for the full period of the shelf-life claim.

10.3 Procedure for estimating shelf-life based upon accelerated stability studies

Pending the completion of real-time stability studies, accelerated stability studies shall be used to estimate the shelf-life. Shelf-life estimates shall be based on a mean kinetic temperature of (30^{+5}_{-2}) °C for all climatic conditions and can be carried out on female condoms from the same production lots as used for real-time determination of shelf-life.

Several approaches to the analysis of accelerated-ageing data have been explored. However, at the date of publication, no single method of analysis was sufficiently validated or widely used to justify its designation as a standard method. The manufacturer can refer to ISO 11346 (Arrhenius testing) or use other validated methods to conduct accelerated shelf-life studies. It is anticipated that as manufacturers and regulatory agencies accumulate real-time data, a consensus method for the next revision of this International Standard will be developed. Meanwhile, the results of accelerated-ageing data can be analysed by a number of methods or as stipulated by the manufacturer's regulatory authority.

NOTE Arrhenius testing cannot be applicable for some types of materials used for the manufacture of female condoms.

Guidance on the conduct and analysis of accelerated ageing studies is provided in Annex L. Data generated from such studies shall support the claim that the female condoms fulfil the requirements of Clauses 9, 11, and 12 and 13.1 for the duration of the labelled shelf-life and at a mean kinetic temperature of (30^{+5}_{-2}) °C.

11 Freedom from holes

When female condoms are tested for freedom from holes in accordance with the method described in Annex J, the AQL and inspection level established in Annex A shall apply. Female condoms with visible holes, and female condoms with non-visible holes greater than 25 mm from the open end are considered non-conforming.

12 Visible defects

When female condoms are tested for visible defects as described in Annex J, the AQL and inspection level established in Annex A shall apply.

13 Packaging and labelling

13.1 Package integrity

When female condom package integrity is tested in accordance with Annex G, the AQL and inspection level established in Annex A shall apply.

13.2 Packaging

Each female condom shall be packed in an individual sealed container. One or more individual containers can be packed in other packaging, such as a consumer package. The individual container, or consumer package or both, shall be opaque to light. The packaging shall protect the female condom from light, even if only the individual package is provided to the consumer. If female condoms are intended to be supplied only in individual containers, the individual containers shall be opaque.

If a marking medium, such as ink, is used on a female condom or on any part of a package directly in contact with a female condom, it shall not have any deleterious effect on the female condom or be harmful to the user.

Individual containers and any other packaging shall protect the female condom from damage or loss of lubricant during normal transportation and storage.

Individual containers and any other packaging shall be designed in such a way that the pack can be opened without damaging the female condom. The design of the individual container should facilitate easy opening.

13.3 Labelling

NOTE National regulations can apply in relation to labelling, especially for latex allergy, etc.

13.3.1 Symbols

If symbols are used on packaging, information, and marketing materials, the symbols shall meet the requirements in ISO 15223 (all parts).

13.3.2 Individual containers

Each individual container shall be indelibly marked with the following information:

a) the identity of the manufacturer or distributor or if permitted by local regulations, the registered brand or trademark;

b) the manufacturer's identifying reference for traceability (e.g. the lot number);

c) the expiry date (year and month). The format of the year shall be in four digits; the format of the month shall be in letters or two digits.

13.3.3 Consumer packages

13.3.3.1 General

The outside of the consumer package shall bear at least the following information in at least one of the official language(s) of the country of destination or as stipulated differently by that country:

a) a statement of identity and intended use, for example: "A female condom is designed to be retained in the vagina during sexual intercourse to prevent pregnancy and transmission of sexually transmitted infections.";

b) a statement of optimal use, which provides specific instructions and/or diagrams on correct use, including how to insert and remove the condom;

c) a statement of limitations: "No barrier methods, including male condoms or female condoms, provide 100 % protection against pregnancy and STIs.";

d) a description of the female condom;

NOTE If the female condom is coloured or textured, this shall be stated.

e) the number of female condoms contained;

f) size designation, if that manufacturer makes more than one size;

g) the name or trade name, country of manufacture, and address of the manufacturer and distributor, subject to national and regional requirements;

h) the expiry date [year and month (The format of the year shall be in four digits and the format of the month shall be in letters or two digits. If a consumer package includes female condoms from different lots, the earliest expiry date shall apply to all female condoms.)];

i) a statement of appropriate storage conditions for the female condom materials;

j) a statement that individual containers, if not opaque to light, shall not be stored outside the opaque consumer package;

k) whether the female condom is lubricated or dry [Whenever a medicinal ingredient is added, it shall be identified and its purpose indicated (e.g. spermicidal). If the female condom or lubricant is fragranced or flavoured, this shall be stated.];

l) the manufacturer's identifying reference for traceability [e.g. the identification number/lot number (If different types of female condoms, e.g. different colours, are packaged together in the same consumer package, the identification number on the consumer package shall allow the manufacturer to identify uniquely the lot numbers of the individual female condoms contained in that package, so that it is possible to trace lots through all stages of manufacture up to packaging.)];

m) a statement for female condoms made of natural rubber latex (NRL) that indicates that the female condom contains natural rubber latex and draws attention to the risks of latex allergy.

13.3.3.2 Additional information for the consumer

The outside or the inside of the consumer package, or a leaflet contained within the consumer package, shall bear at least the following information expressed in simple terms, and in at least one of the official language(s) of the country of destination. If possible, this should also be supplemented by pictorial representations of the major steps involved or as stipulated differently by that country.

a) The package shall bear the instructions for use of the female condom, including:

   1) the need to handle the female condom carefully, including removal from the package so as to avoid damage to the female condom by fingernails, jewellery, etc.;

   2) 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 and pregnancy;

   3) if an additional lubricant is desired, a statement instructing the user to use only the correct type of lubricant that is recommended for use with female condoms;

   4) if the female condom is made with natural rubber latex, a statement instructing the user to avoid the use of oil-based lubricants, such as petroleum jelly, baby oil, body lotions, massage oils, butter, margarine, etc., as these are deleterious to the integrity of the female condom;

   5) a statement instructing the user to consult a doctor or pharmacist about the compatibility of topical medicines that can come into contact with the female condom;

   6) advice to seek medical assistance as soon as possible, at least within 72 h, should a female condom leak or burst during use;

   7) advice that if the individual container is obviously damaged, to discard that female condom and use a new one from an undamaged package;

   8) instructions for withdrawal and disposal of the female condom.

b) The package shall bear a statement that the female condom is for single use only and that cleaning and reuse can compromise the integrity of the device.

c) If the product is manufactured to comply with all requirements of this International Standard, the package shall bear the reference number of this International Standard, i.e. ISO 25841:2013.

13.3.4 Female condoms not distributed in consumer packages

For female condoms that are distributed without a consumer package (e.g. in single foils or strips of foils), it is the responsibility of the organization distributing the female condoms to ensure that adequate information is supplied to the user in accordance with local regulations.

NOTE This information can be in the form of leaflets, training sessions, posters or additional packing added in the distribution chain. For guidance on the content, see 13.3.3.1 and 13.3.3.2.

13.4 Inspection

When inspected, 13 consumer packages and 13 individual containers shall be selected from each lot and examined for conformity to 13.1, 13.2, and 13.3. All inspected containers shall conform to these requirements.

Under certain conditions, the manufacturer/distributor can correct faults associated with packaging and labelling requirements and resubmit the lot for further conformity testing. Examples include insertion of missing instruction leaflets or re-packaging of individual containers into new complete consumer packages before placing them in the market.

If female condoms from the same lot are packed into different consumer packages, at least one consumer package of each variant should be inspected. The number of packages inspected should not exceed 13, unless the number of variants exceeds 13.

14 Data sheets

The manufacturer shall make available to all interested parties a data sheet that contains, for each product variant, at least the following information:

a) specifications for length, width, and thickness;

b) the results of clinical trial lot airburst testing, including the mean bursting volume, the mean bursting pressure, and lower limits for burst pressure and burst volume as calculated in accordance with 9.1;

c) specifications for amount and type of lubricant or powder;

d) list of materials used in the product construction;

e) technical drawing(s) showing female condom geometry and correct locations of fixed retention features;

f) test methods and results for retention features.

Annex A
(normative)

Sampling plans intended for assessing compliance of a continuing series of lots of sufficient number to allow the switching rules to be applied

A.1 Sampling plans and compliance levels

If a party wishes to establish, by inspection and testing of samples of the final product, whether a continuing series of lots are in compliance with the requirements of this International Standard, the sampling plans and acceptance criteria given in Table A.1 shall be applied.

Manufacturers can use the plans in Table A.1 or can devise and implement validated alternative quality control methods that result in at least equivalent consumer protection.

When tests are being conducted on fewer than five lots of female condoms, the additional protection of the switching rules in ISO 2859-1 is not available and it is recommended that the sampling plans given in Annex B be used to maintain the level of consumer protection.

Table A.1 — Sampling plans and acceptance criteria for a continuing series of lots

Attribute	Inspection level[a]	Acceptance criteria
Dimensions	13 female condoms	All samples shall fall within the manufacturers' specified limits.
Bursting volume and pressure	General inspection level I	AQL of 1,5
Package integrity	Special inspection level S-3	AQL of 2,5
Freedom from holes	General inspection level I but at least code letter M	AQL of 0,25
Visible defects	General inspection level I but at least code letter M	AQL of 0,4
Packaging and labelling	13 consumer packages and 13 individual containers	All shall comply.
Quantity of lubricant	13 female condoms	All shall comply.
[a] See ISO 2859-1 where relevant.		

Applications for these sampling plans include the following:

a) ongoing production testing and quality control by a manufacturer;

b) ongoing testing by a purchaser for contractual purposes;

c) ongoing inspection by a national authority.

Annex B
(informative)

Sampling plans intended for assessing compliance of isolated lots

Use of the sampling plans given in Annex A for small numbers of lots, i.e. fewer than five, results in a higher level of consumer risk because the switching rules are not available. In such circumstances, the use of larger sample sizes is recommended in order to maintain an acceptable level of consumer protection. The choice of a suitable sampling plan is governed by cost considerations. Larger sample sizes give better discrimination, but at increased cost. Purchasers can, for example, rely upon their experience with a particular supplier when assessing the sample sizes to use for small numbers of lots.

The sampling plans given in Table B.1, normal inspection, when applied to isolated lots, provide approximately the same level of consumer protection as those given in Annex A when used in conjunction with the switching rules. Attention is drawn to the possibility of using double or multiple sampling plans, which can reduce the total number of female condoms that need to be tested to demonstrate compliance when quality is significantly better than the AQLs.

NOTE There is no simple mathematical relationship between the sample size and the lot size. Sample sizes can be increased independently of the lot size to achieve a more reliable estimate of lot quality.

Table B.1 — Sampling plans and acceptance criteria for isolated lots

Attributes	Inspection[a]	Acceptance criteria
Dimensions	13 female condoms	All samples shall fall within the manufacturers' specified limits.
Bursting volume and pressure	General inspection level I but at least code letter M	AQL of 1,5
Package integrity	Special inspection Level S-3 but at least code letter H	AQL of 2,5
Freedom from holes	General inspection level I but at least code letter N	AQL of 0,25
Visible defects	General inspection level I but at least code letter N	AQL of 0,4
Packaging and labelling	13 consumer packages and 13 individual containers	All shall comply.
Quantity of lubricant	13 female condoms	All shall comply.
[a] See ISO 2859-1 where relevant.		

Applications for these sampling plans include the following:

a) type testing as part of a certification procedure;

b) cases where the total number of lots being assessed is insufficient to allow the switching rules to be effective;

c) in cases of dispute involving isolated lots, e.g. for referee testing.

Annex C
(normative)

Determination of lubricant mass for individual female condom containers

C.1 Principle

The lubricant mass is determined by weighing the packaged female condom, removing the lubricant from the female condom, retention and insertion features, and individual container by washing with a solvent, reweighing the female condom, retention and insertion features, and individual container, and calculating the lubricant mass removed during washing.

C.2 Apparatus

C.2.1 **Ultrasonic cleaning bath(s)**, or suitable container, e.g. beaker and stirrer.

C.2.2 **Balance**, accurate to 1 mg.

C.2.3 **Propan-2-ol**, or other suitable cleaning solvent of laboratory reagent grade depending on the material(s) used in the female condom.

Alternative solvents shall be validated and specified by the manufacturer (hereinafter referred to as "the solvent"). Should alternative solvents be required for either the female condom material or the lubricant material, manufacturers shall specify the solvent to be used.

C.3 Procedure

C.3.1 Weigh each individual closed female condom container to the nearest 1 mg and record the results (m_1).

C.3.2 Slit the individual container carefully around three edges and remove the undamaged female condom.

C.3.3 Remove any retention or insertion features that are not affixed to the female condom.

C.3.4 Before unrolling the female condom, cut up one side using scissors then unroll the female condom and wipe the female condom, removed retention and insertion features, and individual container free of lubricant as much as possible.

C.3.5 When using the ultrasonic bath: immerse the female condom, removed retention and insertion features, and individual container in the solvent in an ultrasonic bath and wash for a period of 2 min to 10 min. Repeat the washing in clean solvent as many times as necessary to achieve constant mass after two successive washes (within 10 mg), after drying as specified in C.3.7 to C.3.8.

C.3.6 When washing the female condoms manually: immerse the female condom, removed retention and insertion features, and individual container in the solvent in a bath and wash with manual agitation. Repeat the washing in clean solvent as many times as necessary to achieve constant mass after two successive washes (within 10 mg), after drying as specified in C.3.7 to C.3.8.

C.3.7 Remove the female condom and individual container from the solvent and wipe to remove excess solvent.

C.3.8 Dry the female condom and individual container to constant mass (within 10 mg) at a temperature not exceeding 50 °C.

C.3.9 Weigh each dry female condom, removed retention and insertion features, and individual container to the nearest 1 mg (m_2).

C.3.10 The total quantity of lubricant for the individually packaged female condom is obtained by subtracting the mass of the female condom, removed retention and insertion features, and package (m_2) from the total mass of the packaged female condom (m_1).

$$m_{tot} = m_1 - m_2 \tag{C.1}$$

C.4 Expression of results

Report the amount of lubricant recovered to the nearest 50 mg.

Annex D
(normative)

Determination of female condom length

D.1 Principle

The unpacked female condom is allowed to hang freely over a graduated mandrel and its length is observed and recorded.

D.2 Apparatus

D.2.1 **Mandrel**, with a scale divided into millimetres.

Each design of a female condom can have unique geometry; therefore, manufacturers shall specify mandrel dimensions that support the closed end of the female condom without distorting the shape of the female condom. The length scale on the mandrel shall begin with zero at the tip of the closed end of the female condom.

D.3 Procedure

D.3.1 Move the female condom inside the unopened package, such that it is away from the area where the package is to be torn. Tear the package and remove the female condom.

Scissors or other sharp instruments shall not be used to open the individual container.

D.3.2 Unpack the female condom, remove any insertion devices, stretch it slightly twice but by no more than 20 mm to smooth out the wrinkles caused by the female condom having been rolled up. Lubricants can be removed and suitable powders can be added to avoid sticking.

D.3.3 Put the female condom over the mandrel and let it hang freely, stretched only by its own mass.

D.3.4 Measure, to the nearest millimetre, the length of the female condom on the scale at the open end. If the measurement varies along the circumference, use the shortest measurement read.

D.3.5 Female condoms subjected to this test can also be used for determination of width.

D.4 Expression of results

Report the length of each tested female condom to the nearest millimetre.

Annex E
(normative)

Determination of female condom width

E.1 Principle

The unpacked female condom is allowed to hang freely over the edge of a ruler and its width is observed and recorded.

E.2 Apparatus

E.2.1 **Ruler**, with a scale divided into millimetres.

E.3 Procedure

E.3.1 Move the female condom inside the unopened package, such that it is away from the area where the package is to be torn. Tear the package and remove the female condom.

Scissors or other sharp instruments shall not be used to open the individual container.

E.3.2 Unpack the female condom and lay it flat over the edge of the ruler, perpendicular to the female condom's axis, allowing it to hang freely. As appropriate, remove any retention features which are not permanently attached to allow the female condom to lay flat. If a lubricated female condom does not hang freely, then the lubricant shall be removed and suitable powders can be added to avoid sticking.

E.3.3 Measure to the nearest 0,5 mm, the width of the female condom at a point or points specified by the manufacturer within 50 mm from the closed end.

E.3.4 Female condoms subjected to this test can also be used for determination of length.

E.4 Expression of results

Report the width of each tested female condom, including the point along the female condom at which the measurement was made.

Annex F
(normative)

Determination of female condom thickness

F.1 Principle

For determining the thickness of the female condom, it is cut open and laid flat. At the midpoint of female condom length, thickness is measured at three equidistant points along the sheath circumference.

F.2 Apparatus

F.2.1 **Flat-footed micrometer**, dial or digital type, measurement intervals of not larger than 0,001 mm, with foot diameter of (5 ± 2) mm, and foot pressure at (22 ± 5) kPa, parallel to a flat base plate.

F.2.2 **Scissors or blade**, for cutting female condoms open.

F.3 Procedure

F.3.1 Move the female condom inside the unopened package, such that it is away from the area where the package is to be torn. Tear the package and remove the female condom.

F.3.2 Remove any insertion device from the female condom and unroll or unfold it, ensuring that it is not excessively stretched in any direction.

F.3.3 Cut the female condom open longitudinally using scissors or a suitable blade.

F.3.4 Wash the female condom in propan-2-ol or other suitable solvent to remove lubricants. Dry the female condom to a constant mass, ±10 mg.

F.3.5 Zero the gauge and measure the thickness of a sample at the midpoint of female condom length. Repeat this measurement two more times and average the three values.

F.3.6 Repeat step F.3.5 at two more points equidistant from one another at the midpoint of female condom length. Point spacing should be chosen such that the three measurement locations would be equidistant from one another along the circumference if the female condom were uncut.

F.3.7 Repeat steps F.3.1 to F.3.6 for the remaining female condom samples.

F.4 Expression of results

Report to the nearest 0,001 mm the average thickness at each of the three points tested for each female condom.

Annex G
(normative)

Testing for female condom package integrity

G.1 General

Individual package integrity refers to the possibility of breaches in sealed individual female condom containers that can result in the leakage of lubricant. Such breaches also cause the package to be permeable to oxygen. However, the test specified in this annex cannot detect leakage due to micro-porosity or gas permeability of the materials used to construct the individual containers. Consequently, this test can be used only to detect leaks large enough to allow leakage of lubricant.

Several tests are under development. Pending conclusive validation that new tests provide greater sensitivity or consistency, package integrity shall be measured in accordance with the following test method (based on ASTM D3078-02) using a vacuum level corresponding to (20 ± 5) kPa absolute pressure.

It is possible that some leaks are not detected by this procedure. Positive pressure inside the female condom container after the vacuum is drawn can force the lubricant, if present, to plug small leaks. The size of the leak that can be detected is dependent upon the lubricant and the nature of the packaging material.

G.2 Test method

G.2.1 Apparatus

G.2.1.1 Vacuum chamber, capable of withstanding approximately one atmosphere pressure differential, fitted with a vacuum-pump, a vacuum gauge, and the possibility to inspect the interior during the test.

G.2.2 Reagent

G.2.2.1 Immersion fluid, water, treated with a wetting agent (such as dishwashing liquid).

G.2.3 Test specimen

Female condoms in their individual containers.

G.2.4 Conditioning

The test sample and test fluid shall be at equilibrium with normal room temperature.

G.2.5 Procedure

Submerge the individual containers in water contained in the vessel within the vacuum chamber. The uppermost surface of the containers shall be covered by not less than 25 mm of water. If a dye is added to the water, leakage of water into the container is easier to detect.

Two or more containers can be tested at the same time, provided they are placed in such a manner that all parts of every container under test can be observed for leakage during the test.

Evacuate the chamber to an absolute pressure of (20 ± 5) kPa. As the vacuum increases, observe the containers for leakage in the form of a steady progression of bubbles. Isolated bubbles caused by

entrapped air are not considered as leaks. Flexible packaging with little or no headspace cannot be reliably evaluated with this test method.

Hold vacuum for 1 min. Release the vacuum, remove the lid, and examine the containers for the presence of water inside.

G.2.6 Interpretation of results

If there are bubbles indicating leaks in a container as the vacuum increases, or if held at specified vacuum, the specimen fails the tests.

If the test fluid is visible inside a container, the container fails the test.

If there are no bubbles observed indicating leaks, and if no test fluid is visible inside a container, the container passes the test.

G.2.7 Test report

When the test is complete, record the numbers of containers with detected leaks.

Annex H
(normative)

Determination of barrier properties using the bacteriophage method

H.1 General

This annex provides the rationale, methodology, and the required sensitivity to test the ability of a female condom to act as a barrier to the transmission of sexually transmitted infections (STIs), including viruses.

A female condom is a medical device designed to be used by a woman to prevent pregnancy and transmission of STIs during sexual intercourse. In order to make a claim that a female condom is effective against STIs, appropriate laboratory tests shall be performed. Since viruses are the smallest aetiological STI agents, the challenge particle should be a small virus or virus-size particle. The challenge particle, solution properties, test pressure, and test duration should be chosen to simulate, as closely as possible, real-use conditions. Choices of parameters that make the *in vitro* test more stringent than expected real-use conditions are encouraged, with appropriate justification. However, movement of the female condom during the test is not required.

The choice of a challenge particle has several important aspects. Signal-to-noise ratio should be considered. A biological assay might be preferred in general because the expected background "noise" signal of a biological assay is less than that of an assay using radioactive or other labelled viruses or virus-like particles.

In order for the test to be used to demonstrate safety with regard to STI barrier properties, the test virus shall be smaller than the hepatitis B virus (42 nm in diameter), the smallest aetiological agent for an STI. Surrogate viruses, such as bacterial viruses (bacteriophages) of appropriate size and shape can be substituted for human pathogens. This protocol suggests use of a small bacteriophage as challenge particle because bacteriophage assays are safe, fast, and comparatively less expensive than alternate assays. Additionally, bacteriophages can be readily obtained at sufficient titre to provide an adequate challenge concentration. The bacteriophage phi-X 174 should be considered as the challenge virus. Other similar challenge bacteriophages can be used, but shall be justified as equivalent to bacteriophage phi-X 174.

H.2 Sample size

Use a minimum of 60 female condoms, 20 from each of three lots, in order to determine acceptability. The comparative female condom for use in the clinical study shall be tested as a control using steps H.4.1 to H.4.5.

H.3 Preparation of test samples

H.3.1 Handle test female condoms carefully so they are not damaged during the test procedure.

H.3.2 Wear gloves as a precautionary measure to prevent abrasion or puncture by fingernails, rings, etc.

H.3.3 Remove any retention and insertion features that are not affixed to the female condom.

H.3.4 Remove the accompanying lubricants and/or spermicides, if present, to prevent interference with the test. Wash and dry the female condom in accordance with steps C.3.5 to C.3.8 to constant mass, ± 10 mg, without damaging the female condom material.

H.4 Procedure

H.4.1 Principle

The test consists of filling the female condom with virus-containing buffer and determining whether any viruses penetrate the female condom barrier during submersion in a collection buffer. Virus penetration is quantified and reported as the equivalent volume of penetrating challenge buffer needed to account for the amount of virus penetration into the collection buffer. Positive control experiments of the same duration are needed to ensure that the overall test is functioning properly.

H.4.2 Test apparatus requirements

H.4.2.1 The test apparatus shall provide a leak-proof seal at the female condom open end and leave an appropriate length of test portion available for the virus penetration test.

H.4.2.2 The apparatus shall restrain the female condom to prevent over-expansion under pressure. Dimensions of the restraining device should allow for expansion of the test portion of the female condom to a length greater than the length of the test female condom and a circumference appropriate for the female condom material tested. The contour of the restraining device should approximate that of the female condom. Restrainers of the same size and material should be used with the test female condoms and with the comparative female condoms.

H.4.2.3 The apparatus shall provide for exposure of the inside of the female condom to aqueous challenge virus suspension.

H.4.2.4 The apparatus shall provide for application of pressure to that suspension.

H.4.2.5 The apparatus shall allow for submersion of test portion of female condom in collection fluid.

H.4.2.6 The apparatus shall provide for access to challenge virus suspension inside female condom for assay following the test.

H.4.3 Buffer requirements

H.4.3.1 The challenge buffer solution and the collection buffer solution shall have a pH value of approximately 7.

H.4.3.2 The challenge buffer solution and the collection buffer solution shall have salinity of any one of several variations of physiological saline.

H.4.3.3 The challenge buffer solution and the collection buffer solution shall have surface tension less than 0,05 N/m.

H.4.3.4 The challenge buffer solution shall contain the challenge virus at adequate titre at the beginning of the test so that even at the end of the test the titre is sufficient. Sufficient titre for a small, approximately spherical virus is at least 10^8 plaque forming units/ml.

NOTE One adequate buffer is 0,1 % Triton X-100®[1)]. Physiological saline has a lower viscosity than semen and therefore provides a more stringent test.

The test can be performed at room temperature (25 + 2) °C when saline is used.

H.4.4 Sample testing

H.4.4.1 Fill the female condom with the challenge buffer.

H.4.4.2 Apply pressure to the internal volume of the female condom, such that the pressure of the challenge fluid is equivalent to 8 000 Pa.

H.4.4.3 Place the female condom in a collection container with sufficient buffer to allow fluid contact with the test surface of the female condom and to collect any virus that penetrates through the female condom.

H.4.4.4 Submerge the filled, pressurized female condom in the collection buffer for at least 30 min.

H.4.4.5 Mix the collection fluid just prior to assaying so that the assay aliquots are representative.

H.4.4.6 Assay the collection buffer for the challenge virus to determine whether any virus has penetrated the female condom and passed into the collection buffer.

H.4.4.7 Calculate the equivalent volume of challenge virus penetration needed to account for amount of virus found in collection buffer.

H.4.5 Positive control testing

Use positive controls that meet requirements a) to e).

a) Follow the same procedure in H.3 and H.4.4 using female condoms with representative pinholes placed using a small gauge needle, of approximately 30 µm in diameter, laser, or other suitable method. Female condoms with intentional pinholes can be used, although it is recognized that it is difficult to produce small pinholes.

b) Verify stability of virus concentration. Determine whether the challenge virus remained at a stable concentration in the female condom during the test. Data from several positive control female condoms shall be collected as part of each female condom test. The titre of the challenge virus suspension inside the female condom at the end of the test is compared to the titre originally placed in the female condom. This determines if and how much the challenge virus titre changes during the test because of interaction with the female condom and the test apparatus, or other factors.

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

d) Increase the starting titre of the challenge virus if the stability controls and/or the detection controls indicates the loss of virus titre below 10^8 plaque forming units/ml to compensate for the loss and to maintain the overall sensitivity of the test.

1) Triton X-100® is an example of a suitable product available commercially. This information is given for the convenience of users of this International Standard and does not constitute an endorsement by ISO of this product.

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

H.5 Detection limits and reporting

H.5.1 Detection limit explanation

H.5.1.1 For a 95 % confidence that an assay finds at least one virus when virus is present [i.e. $P(0) < 0{,}05$], the average number of infectious particles per total volume assayed shall be at least three; e.g. there is a 95 % probability that a titre of 1 pfu/ml results in at least one plaque in a 3 ml total assay. Thus, the sensitivity or detection limit of this assay can be claimed as 1 pfu/ml when 3 ml is assayed.

H.5.1.2 Detection limit expressed as volume of challenge virus suspension that penetrated the barrier is probably the most useful measure of test sensitivity. For example, in a real-life risk assessment, the volume of transmitted virus-containing fluid can be translated into infectious units when the titre of a pathogenic virus (in real life) is known.

H.5.1.3 The test procedure shall be able to detect 2×10^{-6} ml penetration of the challenge virus suspension. This can be done by

a) using a challenge buffer titre of 1×10^{8} pfu/ml,

b) using a collection buffer volume of 200 ml, and

c) assaying 1 ml in triplicate from the collection buffer (assuming no loss of virus titre in the challenge buffer nor in the collection buffer): the assay detection limit of 1 pfu/ml is equivalent to penetration by 200 pfu (1 pfu/ml × 200 ml) or 2×10^{-6} ml (200 pfu divided by 1×10^{8} pfu/ml).

H.5.2 Detection limit analysis

H.5.2.1 Assay at least 1 ml in triplicate (3 ml total).

H.5.2.2 Present the individual results for each female condom sample tested in a table that includes

a) the challenge buffer virus titre,

b) the virus titre in the collection buffer,

c) any correction factor for loss of virus (determined in the controls), and

d) the calculated challenge volume that penetrated (for the female condoms that allowed virus transmission). This value of the volume of challenge virus suspension needed to account for the virus penetration into the collection buffer can be calculated for each female condom by the method presented in the previous section. If some loss of virus titre occurs either inside the female condom or outside in the collection container, the calculation should include the appropriate correction for such loss. For female condoms that apparently did not allow virus transmission, the detection limit of that particular test should be given, e.g. as 2 × 10−6 ml.

H.5.3 Reporting

H.5.3.1 Positive control

Reporting the results of the positive control experiment should be done using the same reporting format as with virus penetration of test samples in H.5.3.3.

H.5.3.2 Challenge virus stability

Results from the test of challenge virus stability should be presented in tabular form, where the data for each female condom are individually reported. Necessary items for each test sample are

a) the date the test was performed,

b) the titre of challenge buffer placed inside the female condom at the beginning of the test,

c) the titre of challenge buffer inside the female condom at the end of the test, and

d) the calculated ratio of final to beginning titre.

H.5.3.3 Challenge to virus detection

Results from tests to determine the detection of penetrated virus should be in tabular form, where the data for each female condom are individually reported. Necessary items for each test sample are

a) the date the test was performed,

b) the titre of collection buffer at the beginning of the test,

c) the titre of collection buffer at the end of the test, and

d) the calculated ratio of final to beginning titre.

Annex I
(normative)

Determination of bursting volume and bursting pressure

I.1 Principle

A specified length of the female condom is inflated with air, and the volume and pressure required to burst the female condom are measured and recorded.

I.2 Apparatus

I.2.1 Inflation apparatus, suitable for inflating the female condom with clean oil-free and moisture free air at a specified rate, provided with equipment for measuring air volume and pressure and having the following features.

It is the female condom manufacturer's responsibility to provide inflation apparatus specifications that are unique to that specific female condom design:

a) a pressure sensor configured such that there is no pressure differential between the female condom and the pressure sensor;

b) an apparatus for recording the volume of inflation air, configured such that there is no pressure differential between the measuring device and the female condom, thereby ensuring that the volume of the air is measured or calculated at the appropriate pressure within the female condom and not at the line pressure which might be higher;

c) rod of suitable length (approximately the nominal female condom length specified by the manufacturer) having a smooth sphere or hemisphere at its top for hanging the unrolled female condom without distortion of the female condom when fixed to the apparatus, and fixed in a position such that when the female condom is clamped, it allows the maximum amount of the device to be inflated and is no less than the rod length range specified by the manufacturer;

d) pressure and volume measuring equipment capable of

   1) a maximum permissible limit of error of ±3 % for volumes greater than 10 dm^3, whatever method is used to measure the volume, and

   2) measuring the pressure at burst of the female condom with a maximum permissible limit of error of ±0,05 kPa.

I.2.2 Clamping apparatus, for example, a clamping ring, having no sharp edges or protrusions.

It is the female condom manufacturer's responsibility to provide clamping apparatus specifications that are unique to that specific female condom design. The recommended material of construction is non-brittle transparent plastic. The clamping ring should not stretch the female condom as the clamping ring is placed on its mount.

I.2.3 Inflation cabinet, having the facility for viewing the female condom during inflation, and of sufficient size to allow the female condom to expand freely without touching any part of the cabinet.

I.3 Procedure

I.3.1 Carry out the test under controlled temperature of (25 ± 5) °C and relative humidity (55 ± 15) %.

I.3.2 Move the female condom inside the package such that it is away from the area where the package is to be torn. Tear the package and remove the female condom. Scissors or other sharp instruments shall not be used to open the individual container.

I.3.3 It is recommended that suitable gloves or finger cots be worn while handling the female condom. In cases of dispute, gloves shall be worn.

I.3.4 Remove the retention features carefully from the female condom, if possible.

I.3.5 Hang the female condom on the test mount (rod) and secure the base of the female condom with the clamping device.

I.3.6 Take care when placing the clamping device on its mount to avoid damaging or stretching the female condom. Inflate with air at a rate specified by the manufacturer. When no rate is specified, use a rate of 0,4 dm^3/s to 0,5 dm^3/s (24 dm^3/min to 30 dm^3/min).

I.3.7 Check to ensure that the female condom expands and there are no obvious leaks.

I.3.8 If the female condom exhibits any obvious leak or leaks are detected during the inflation, discontinue the test. The female condom is deemed to fail the test and the bursting volume and pressure are recorded as zero.

I.3.9 If the female condom does not leak, measure and record the bursting volume, in cubic decimetres rounded to the nearest 0,1 dm^3 if the minimum burst volume is below 15 dm^3, and to the nearest 0,5 dm^3 if the minimum burst volume is above 15 dm^3 or above. The bursting pressure, in kilopascals, shall be rounded to the nearest 0,05 kPa.

I.4 Expression of results

Record the bursting volume and bursting pressure of each tested female condom.

Annex J
(normative)

Testing for holes

J.1 General

This annex specifies the water leak method for testing female condoms for visible and non-visible holes and visible defects.

J.2 Water leak test

J.2.1 Principle

Female condoms are visually inspected then filled with water and examined for visible water leakage through the wall of the suspended female condom. In the absence of any leakage, the female condom is then rolled on a coloured absorbent paper which is subsequently examined for signs of leakage of water from the female condom. Female condoms can be tested with or without the external retention device.

J.2.2 Apparatus

J.2.2.1 Water leak test plug, suitable for filling the condom with water while suspended and having a watertight fit with the open end of the female condom with or without the external retention device and a stopper to prevent water loss.

An informative example is shown in Figure J.1 (each female condom manufacturer shall make available upon request the critical dimensions appropriate for each female condom design). The plug can have a tapered shape that extends into the female condom volume to aid the technician in guiding the external retention feature onto the test plug. This feature shall allow as much as possible of the open end to be tested and inspected.

J.2.2.2 Water leak testing rack, suitable for allowing the female condom to be freely suspended by the test plug as shown in Figure J.2.

J.2.2.3 Absorbent towel.

J.2.2.4 Coloured absorbent paper.

J.2.2.5 Gloves.

J.2.2.6 Water.

J.2.2.7 Test rack.

J.2.2.8 Stopwatch.

J.2.3 Preparation

J.2.3.1 Wear suitable gloves when handling the female condoms so as to avoid damage to the female condom by fingernails, jewellery, etc.

J.2.3.2 To remove the female condom from its packaging, move the female condom inside the individual container such that it is away from the area where the individual container is to be torn. Tear the individual container and remove the female condom. Scissors or other sharp instruments shall not be used to open the individual container.

J.2.3.3 Unroll the female condom and remove any non-permanently attached retention features.

J.2.3.4 Inspect the entire female condom for visible holes as defined in Clause 3. If any hole or tear is noticed, the female condom shall be deemed non-conforming and further testing of that female condom shall be discontinued.

J.2.3.5 Inspect the entire female condoms for visible defects as defined in Clause 3. If any visible defect other than a visible hole is noticed, the female condom shall be deemed non-conforming with respect to visible defects and further testing of that female condom shall be discontinued. If the defect is a visual hole, the female condom shall be deemed non-conforming with respect to freedom from holes and further testing of that female condom shall be discontinued.

J.2.4 Procedure

J.2.4.1 Fit the female condom external retention feature around a water test plug as shown in Figure J.2. Ensure the external retention feature is properly fitted on the test plug to ensure a leak-free seal. If visible abrasions or damage to the female condom are introduced during this fitting procedure, do not continue testing the female condom, move it to the drying rack and record that the female condom was not tested.

J.2.4.2 Fill the female condom with water at 10 °C to 40 °C. Intermittently tap the female condom to dislodge air bubbles, and top off until the solution rises to the top of the test plug. Insert the rubber stopper to seal the plug.

J.2.4.3 Dry the outside surface of the female condom with an absorbent towel. Inspect the female condom for leaks.

J.2.4.4 Suspend the female condom in the test rack as shown in Figure J.2 for a minimum of 1 min. Following the suspension, visually inspect for any signs of leakage.

J.2.4.5 Remove the female condom and test plug from the test rack. If no holes have been detected, roll the filled female condom on coloured absorbent paper and inspect for leaks as shown in Figure J.3. Suspend the test plug over the edge of the testing table to maximize contact between the female condom and paper. Use even and firm hand pressure. Complete at least one whole rotation in each direction.

J.2.4.6 Examine the coloured absorbent paper for signs of leakage. If wet patches appear on coloured absorbent paper, locate the source of the leak. Continue the rolling until the leak has been found or it is determined that the initial wet patch was introduced by a means other than a female condom leak.

J.2.4.7 Twist the female condom just below the midway position to create two sections of the filled female condom as shown in Figure J.4. Press the female condom distal end into the coloured absorbent paper to ensure all female condom surfaces are tested as shown in Figure J.5. Examine the coloured absorbent paper for signs of leakage as described above in J.2.4.6. Record all results.

J.3 Interpretation of test results

Female condoms with visible holes and visible defects, and female condoms with non-visible holes greater than 25 mm from the open end are considered non-conforming.

J.4 Test report

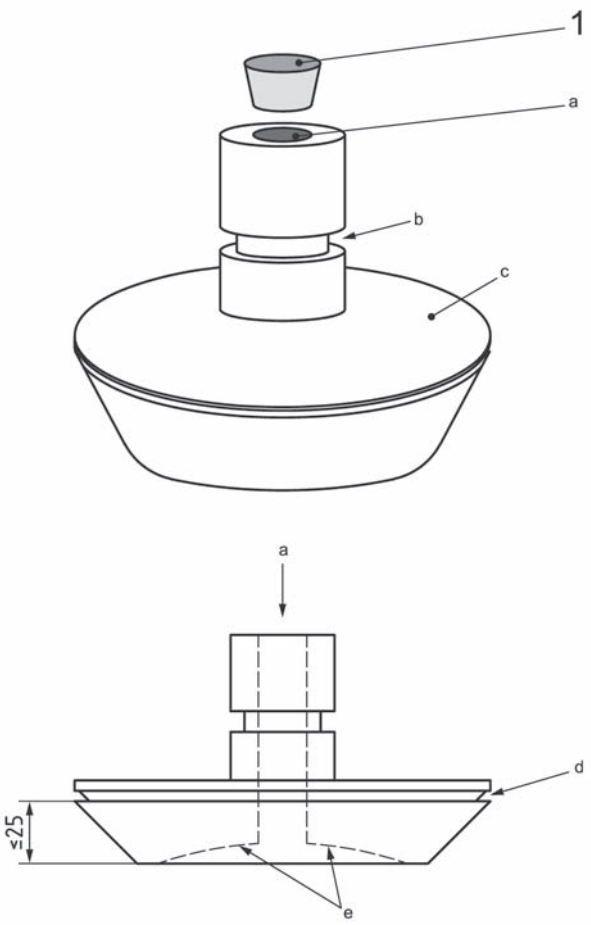
Upon completion of the test, record the following data:

a) the number of female condoms tested;

b) the number of condoms with visible or non-visible holes located;

c) the number of condoms with visible defects observed.

Dimensions in millimetres



Key

1 stopper

a Filling orifice.

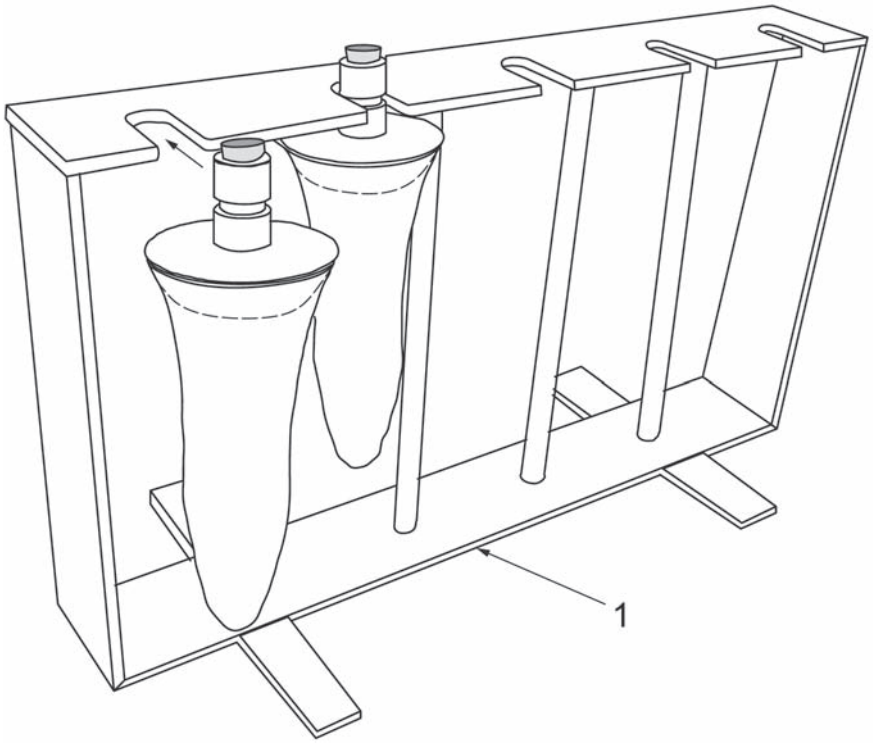
b Testing rack groove.

c Water leak test plug.

d Groove geometry sized to fit specific device external retention feature.

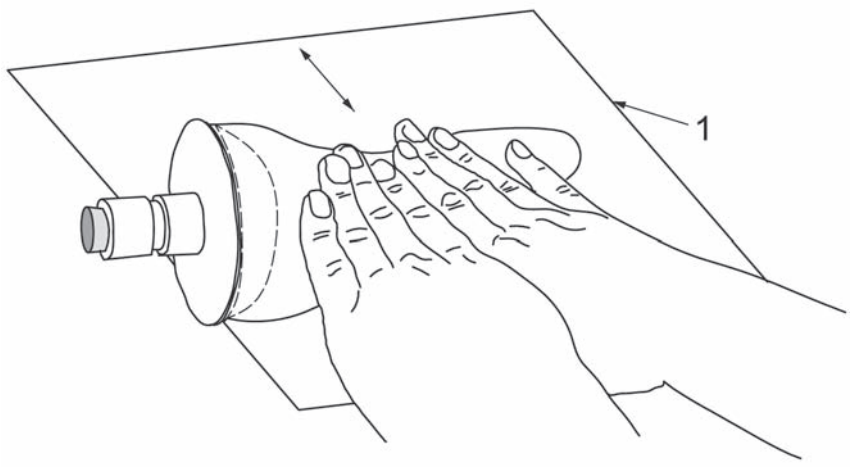
e Dashed lines indicate preferred geometry to allow air bubbles to escape.

Figure J.1 — Example of a test plug with rubber stopper



Key
1 water leak testing rack

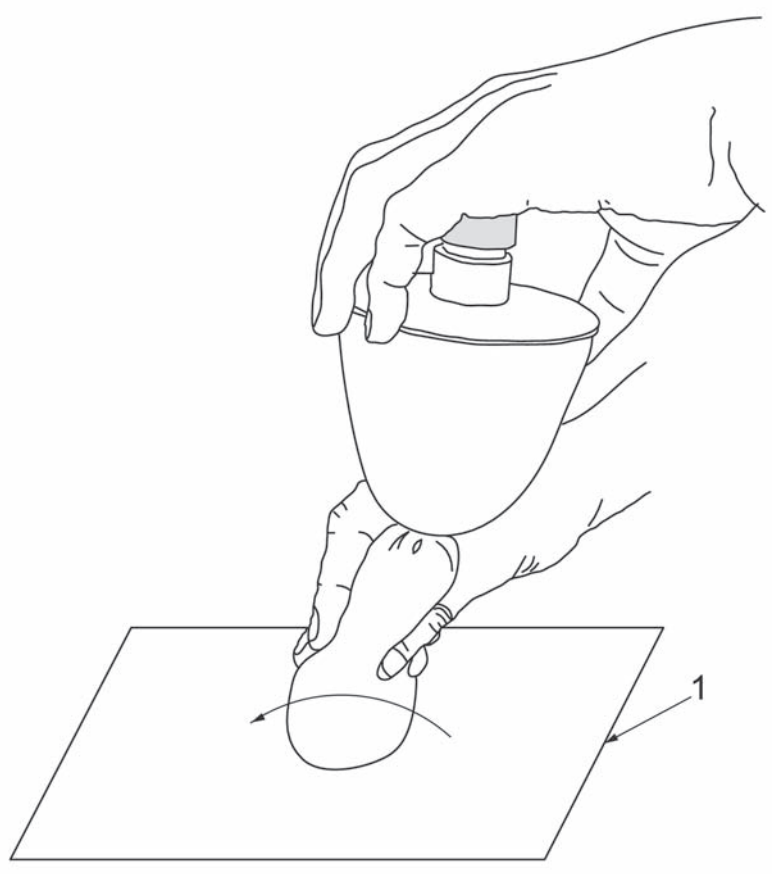
Figure J.2 — Example of a water leak testing rack



Key
1 coloured absorbent paper

Figure J.3 — Example of a rolling filled female condom with test plug on absorbent paper

Figure J.4 — Example of twisting the female condom



Key
1 coloured absorbent paper

Figure J.5 — Example of testing the distal end of the female condom

Annex K
(normative)

Determination of shelf-life by real-time stability studies

K.1 Principle

To simulate storage conditions worldwide, packaged female condom samples are oven-conditioned at $\left(30^{+5}_{-2}\right)$ °C for the intended shelf-life period. Following the conditioning, the samples are then subjected to testing for conformance with the airburst, freedom from holes, visible defects, and package integrity requirements of Clauses 9, 11, and 12 and 13.1. To monitor changes during the ageing period, samples shall also be subjected to the same testing at regular intervals before the end of the intended shelf-life.

K.2 Procedure

K.2.1 General

After determining conformity to Clauses 9, 11, and 12 and 13.1, sufficient female condoms shall be placed in a controlled environment and conditioned at (30^{+5}_{-2}) °C. Shelf-life shall be confirmed if female condoms meet the requirements of Clauses 9, 11, and 12 and 13.1 after conditioning for a period equal to the intended shelf-life claim.

K.2.2 Conditioning

K.2.2.1 Condition samples from three lots of female condoms packed in their respective individual containers at (30^{+5}_{-2}) °C.

K.2.2.2 Condition enough female condoms per lot to ensure sufficient samples (at least 32) can be tested for conformity to Clause 9 at intervals of one year or less over the duration of the proposed shelf-life period.

K.2.2.3 Condition enough female condoms per lot to ensure sufficient samples can be tested for conformity to Clauses 9, 11, and 12 and 13.1 at the end of the proposed shelf-life period, in accordance with sample sizes required in Annex B.

Although the suggested minimum is 200 female condoms, it is strongly recommended that additional female condoms be conditioned as spares in case there is a need for any re-testing or in case additional time points are required.

K.2.3 Testing

K.2.3.1 Remove sample female condoms from the controlled environment at intervals determined according to K.2.2.2.

K.2.3.2 Determine the bursting volume and pressure in accordance with Annex I. Plot the mean and standard deviation of the bursting pressure and volume against time for each lot. At the end of the proposed shelf-life period, or if the mean and standard deviation of the burst properties deteriorate to the point where the female condoms might be approaching the limit of complying with the air burst requirements

of 9.1, test sufficient female condoms per lot using the sampling plan in Annex B for bursting volume and pressure in accordance with Annex I. Assess conformity to the air burst requirements of 9.1.

K.2.3.3 Determine freedom from holes in accordance with Annex J and assess conformity to the requirements of Clause 11.

K.2.3.4 Determine visible defects in accordance with Annex J (J.2.3.3 and J.2.4.1) and assess conformity to Clause 12.

K.2.3.5 Determine package integrity in accordance with Annex G and assess conformity to the requirements of 13.1.

K.3 Confirmation of shelf-life claim

Upon completion of K.2, the shelf-life claim shall be up to that period, not to exceed 5 years, for which the female condoms have complied with the requirements of Clauses 9, 11, and 12 and 13.1.

If the labelled shelf-life is more than the confirmed shelf-life, the manufacturer shall adjust the shelf-life claim and notify the regulatory authorities and direct purchasers.

K.4 Test report

Report the following:

a) the individual bursting volume and pressure results for each of the female condoms at all the times tested;

b) the plot of average bursting pressure and volume against time, number of non-conforming units, and distribution curves;

c) the freedom from holes and visible defects results for each lot, as determined according to J.3;

d) the package integrity and labelling results from each lot, as determined according to G.2.6;

e) the confirmed shelf-life claim.

Interim test reports shall be made available to appropriate regulatory bodies on request, to document that the real-time study has begun.

Annex L
(informative)

Guidance on conducting and analysing accelerated ageing studies

L.1 Principle

Accelerated ageing studies can be used to estimate provisional shelf-life. This annex describes general protocols that can be used for conducting accelerated ageing studies to estimate shelf-life for market introduction while real-time studies are in progress. It also offers guidelines on analysing these studies to predict shelf-life.

L.2 Background

Before commencing accelerated ageing studies, consideration should be given to the specific mechanisms of degradation that can apply to the type of materials used to fabricate the female condom. Some materials, for example, can exhibit excellent resistance to thermal and oxidative degradation, but can be susceptible to rapid degradation by hydrolysis if not protected from moisture. Accelerated ageing studies are usually undertaken at elevated temperatures to increase the rate of degradation, but other potentially important factors, such as humidity, also need to be taken into account.

It should also be recognized that the use of high temperatures can cause effects to occur that are not relevant to the normal ageing processes observed under ambient conditions. For example, some thermoplastic materials can exhibit excessive softening or partial melting at elevated temperatures.

Certain materials, e.g. natural rubber latex, have multiple degradation mechanisms which are exhibited to different degrees at different temperatures. The manufacturer should characterize the materials used for the design of the female condom to best determine which method is best for conducting and analysing accelerated ageing studies.

Because of the variety of designs and materials utilized in female condoms, where possible, manufacturers are encouraged to develop and validate methods based on historical trend analysis for products of the same formulations.

L.3 Procedure for conducting accelerated ageing studies

Condition the female condoms from three production lots in ovens at selected temperatures. At appropriate time intervals, remove samples of female condoms from the oven and determine the air bursting properties in accordance with Annex I, and test for holes in accordance with Annex J. It is recommended that a minimum of four elevated temperatures be used. A minimum of five time points at each temperature is recommended and the study should continue for at least 120 days and preferably 180 days. It is recommended that at least 32 female condoms be tested at each time for each temperature point.

If the results are going to be compared with those for a female condom for which real-time stability data are available, equivalent samples of that female condom should be conditioned at the same time. If no methods have been validated by the manufacturer, the minimum test requirement is to age the female condoms for 180 days at 50 °C.

L.4 Analysis of accelerated ageing data to estimate provisional shelf-life

For many products, shelf-life estimates can be predicted by extrapolation from accelerated ageing studies using the Arrhenius equation. Details of the procedure are given in ISO 11346. The application of the Arrhenius plot should be considered first. The Arrhenius equation cannot be applicable for some types of materials used for the manufacture of female condoms.

In some cases, it is possible that the Arrhenius plots are not linear. Several approaches to the analysis of nonlinear Arrhenius-type plots have been explored and it is anticipated that as manufacturers and regulatory agencies accumulate real-time data, a consensus method will be developed. It is emphasized that any attempt to extrapolate shelf-life estimates from nonlinear Arrhenius plots carries a high level of risk and manufacturers should be conservative about any estimates made under such conditions.

A convenient method of presenting and analysing stability data are to use the time-temperature superposition method (also called the WLF method) to superimpose data from different temperatures on to a single master curve. This method is also described in ISO 11346. In this procedure, the time values for each data point are transformed to equivalent times at a common reference temperature by multiplying the time values by the Arrhenius shift factor, a_T, which is derived from the Arrhenius equation:

$$a_T = \exp\left\{\frac{E_a\left(1/T_{ref}\right) - \left(1/T_{age}\right)}{R}\right\} \quad \text{(L.1)}$$

where

E_a is the activation energy;

R is the gas constant (8,314 472 J/(mol K);

T_{ref} and T_{age} are the reference and ageing temperatures, respectively, in kelvins.

The reference temperature for female condom stability studies is 30 °C.

The physical properties obtained at the various ageing temperatures are plotted against the respective transformed times on a common graph. If the ageing properties transform according to the Arrhenius equation and the correct value is used for the activation energy, then a single master curve is obtained. The properties of the female condom after any period of ageing at the reference temperature can be readily read off the resulting curve. Alternatively, the shift factor can be determined by using the least squares method to find the best value of a_T to maximize the overlap of the curves or, if the data are plotted on a log time basis, simply by sliding the degradation curves along the log time axis until the best overlap is observed visually.

Yet another method of analysing stability studies is to compare the rates of change of burst properties with those of a female condom of similar formulation for which the shelf-life has already been determined by a real-time study.

The results of accelerated ageing data can be analysed using any of the methods described above, any other appropriate method, or as stipulated by the manufacturer's regulatory authority. The method chosen, if not based on the Arrhenius procedure, should be justified. Manufacturers are not limited to the specific methods described above (see L.4) and are encouraged to investigate these and other methods.

L.5 Test of shelf-life estimates

Once the shelf-life of the female condom has been estimated, it is necessary to confirm that female condoms selected from three lots comply with the airburst and freedom from holes requirements of Clauses 9 and 11 after completion of the thermal challenge equivalent to the proposed shelf-life at 30 °C. Select a set of accelerated ageing conditions equivalent to the estimated shelf-life at the proposed

climatic temperature. The ageing conditions should be chosen with a view to replicating the mode of failure at 30 °C that is predicted by the stability study.

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