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Female condoms — Use of ISO 25841 and the quality management of female condoms

Préservatifs féminins — Utilisation de l'ISO 25841 et du management de la qualité des préservatifs féminins

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Contents

Page

Foreword ..... **iv**
Introduction ..... **v**
1 Scope **1**
2 Normative references **1**
3 Terms and definitions **1**
4 Quality of design **2**
4.1 General 2
4.2 Design input and design development 2
4.2.1 General 2
4.2.2 Barrier sheath 3
4.2.3 Product insertion feature and retention feature 3
4.2.4 Dressing materials 4
4.2.5 Lubricants 4
4.2.6 Biocompatibility 4
4.2.7 Control of bioburden 4
4.2.8 Packaging 4
4.3 Design verification 5
4.4 Design validation 5
4.4.1 Evaluation of barrier properties 5
4.4.2 Clinical (human use) investigations 5
4.4.3 Stability studies and shelf-life claim 5
4.5 Design output 6
4.5.1 General 6
4.5.2 Details of materials 6
4.5.3 Specifications of the female condoms 6
4.5.4 Supporting information 7
4.5.5 Regulatory compliance 7
4.6 Design transfer 7
4.7 Validation and change controls 7
5 Risk management **7**
6 Quality in manufacture **8**
7 Quality in testing **10**
7.1 General 10
7.2 Test equipment 11
7.3 Sampling and testing: 11
7.4 Training and competence of personnel in testing 11
7.5 Review of results and reports: 11
8 Quality in procurement **12**
9 Handling and disposal of used female condoms **12**
Bibliography **13**

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing Technical Reports 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 of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 157, *Non-systemic contraceptives and STI barrier prophylactics*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

A female condom is a sheath that completely lines the vaginal canal and is designed 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).

Female condoms that meet or exceed the requirements of ISO 25841 are effectively used for contraceptive purposes and in the prevention of sexually transmitted infections (STIs). They have adequate barrier properties, adequate physical properties so as not to break during use, are correctly packaged to protect them during storage throughout the claimed shelf life and are correctly labelled to facilitate their correct use.

ISO 25841 is a quality standard for female condoms, detailing the requirements for establishing the baseline specifications and for testing the finished product for compliance to the predefined specifications. It is applied by manufacturers, procurement agencies, regulatory bodies, and testing laboratories.

ISO 13485 is a generic standard for quality management of medical devices and serves as the requirement for regulatory compliance. The specific quality requirements for female condoms are given in ISO 25841. This document is a document providing manufacturers, buyers, regulatory agencies and third-party test laboratories, information relating to implementation and application of ISO 25841 and ISO 13485 in the quality management for manufacture of female condoms, and for purchasers to develop appropriate purchase technical specifications and to verify that condoms delivered comply with requirements of ISO 25841 and ISO 13485. This document outlines the importance of the requirements of the quality management system based on ISO 13485 that are applied during all the stages of design and development, production, supply, procurement, and post- production related to the complete life cycle of female condoms.

Consistent quality of female condoms, as other medical devices, is achieved by implementation of quality management system as per ISO 13485, which enables that quality is built into the product and assured at every phase in the design, planning, production, procurement processes and post-production activities. The requirements of ISO 13485 include implementation of the requirements ISO 14971 on risk management during all the phases of manufacture.

Female condoms, being medical devices, are subject to regulatory controls by national and regional regulatory agencies. The regulations address both the aspects of product approval and registration and licensing controls on the manufacture and distribution of female condoms. Compliance with the requirements of ISO 13485 and ISO 25841 are essential aspects which form the basis of regulatory approvals.

The specific additional requirements of buyers and consumers are specifically given due consideration when complying with the requirements of ISO 25841, as ISO 25841 is general by design, based on the designs that are currently approved for marketing. There are also specific documented technical specifications such as WHO UNFPA technical Specification on female condoms, which address the requirements of projects and procurement for public distribution programs.

The designs of female condoms, which are currently available in the market or under development, vary considerably with reference to the design of the sheath, the type of retention features, dressing materials, lubricants, etc. Thus, the failure modes of each design of female condom could vary significantly. Therefore, ISO 25841 requires that the efficacy and the safety of each design of female condoms should be substantiated by

a) preclinical evaluations which would include standardization of physical properties, assessment of barrier properties, tests for stability and shelf life and assessment of biocompatibility to ensure the safety of materials that are used in the manufacture of female condoms and their components such as sheath, retention features, dressing materials, lubricants, additives, residual processing aids, etc. as prescribed in ISO 25841, and

b) clinical investigations in humans to establish the efficacy and in vivo safety, as prescribed in ISO 25841, ISO 29943-2, ISO 10993-1, ISO 10993-5 and ISO 10993-10 and if necessary, ISO 10993-3.

Though female condoms are non-sterile medical devices, manufacturers are recommended to implement appropriate measures to minimize microbiological contamination of the product, by exercising controls on the components used in the manufacture of female condoms, manufacturing environment during manufacture of sheath, assembly of condoms and their packaging, manufacturing operations and health and hygiene of personnel.

It is important that properties of female condoms are maintained throughout the shelf life to ensure their safety and efficacy. ISO 25841 requires that the shelf life of any new or significantly modified female condom should be estimated by conducting stability studies as per ISO 25841 and, based on such studies, the appropriate storage conditions should be prescribed. The review of data of the shelf studies is important for granting product approvals and for awarding purchasing requirements.

This document also addresses how to deal with other important issues not directly covered by ISO 25841, but related to effective implementation of quality management system in manufacture of female condoms which will conform to the specifications of ISO 25841.

Female condoms — Use of ISO 25841 and the quality management of female condoms

1 Scope

This document gives the essential principles in the application of ISO 25841. It outlines the details of elements applicable in quality management of female condoms as required by related normative standards, as referred in ISO 25841 and other relevant concepts.

This document supplements the use of ISO 25841 and addresses quality management aspects to be considered during the development, manufacture, quality verification and procurement of female condoms. It encompasses the principles of quality management systems in design, manufacture, and delivery of female condoms with emphasis on their performance, safety and reliability.

This document is applicable to female condoms made of natural rubber or synthetic rubber or synthetic polymers and the retention devices which form the integral components of female condoms.

NOTE Female condoms made from either natural rubber latex or synthetic rubber or other synthetic polymeric materials are addressed in ISO 25841.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes references for this document. 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, *Sampling procedures for inspection by attributes — Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection*

ISO 9000, *Quality management systems — Fundamentals and vocabulary*

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

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

ISO/IEC 17025, *General requirements for the competence of testing and calibration laboratories*

ISO 25841, *Female condoms — Requirements and test methods*

ISO 29943-2, *Condoms — Guidance on clinical studies — Part 2: Female condoms, clinical function studies based on self-reports*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 2859-1, ISO 9000, ISO 13485, ISO 14971, ISO/IEC 17025, ISO 25841 and ISO 29943-2 apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

4 Quality of design

4.1 General

Female condoms essentially comprise of the following components: sheath, which is made of natural rubber latex or synthetic rubber or other synthetic polymer material with an external retention device (retention feature) and where applicable, an internal retention device (product insertion feature). The dimensions of the barrier sheath and insertion features may vary depending on the proprietary designs, which have been validated for their safety and efficacy. The lubricant used in the female condoms also vary with the design of the manufacturers. Because of such a wide variety of the design and the materials, the unique features and characteristics specific design are detailed in the product Data sheet (see 4.5).

The following features/characteristics have been listed in ISO 25841:

a) product insertion into the vagina;

b) product retention and prevention of slippage during sexual intercourse or penile removal;

c) penile misdirection during sexual intercourse;

d) invagination of the female condom during sexual intercourse;

e) safe product removal after sexual intercourse;

f) safety of all materials used in the construction of the female condom including the risk of any interaction between the materials;

g) impermeability of the film to microorganisms;

h) risk of breakage of the female condom during insertion, use and withdrawal.

4.2 Design input and design development

4.2.1 General

The requirements of design and development as prescribed in ISO 13485 are applicable in the design and development of female condoms. When the design and development activities relating to female condoms conform with the requirements of ISO 13485, the dimensions and shape of the female condoms and their components are appropriate for the anatomy and physiology of female and male reproductive organs and are proven to be functionally suitable for the efficacy of female condoms. Survey of clinical literature supported with laboratory scale development and evaluation of several prototypes enables that the female condom design fulfils the above criteria. Currently, several types of designs having shapes such as tubular, dome shaped, cylindrical, etc. with different types, material of construction and geometry of the external and internal retention features are available. The designs of the female condoms are not limited to the above and several innovative designs are under development. The designs of female condoms are mostly patented. While evaluating the options, it is important that the basis of evaluation takes into consideration the following potential failure modes listed in ISO 25841:

1) acute failure event;

2) clinical breakage;

3) non-clinical breakage;

4) total breakage;

5) clinical slippage;

6) clinical misdirection;

7) clinical invagination;

8) total clinical failure;

9) total female condom failure.

In addition to the given failure modes, other potential new failure modes which are identified during the risk assessment of design and development also play a vital role in development and validation of the design. It is quite possible that during the initial controlled clinical evaluations, additional information on the suitability of the designs will be available to be used for progressing further the development of the designs. Due to anthropometric variations of male and female reproductive organs, the optimal designs can have a range of dimensions and shape of the female condoms. The data sheets and labels of female condoms depict the essential features of dimensions and design of the specific type of female condoms.

Continual survey of technical information and reports on post-market clinical follow up and surveillance help keeping the design of the female condoms 'state-of-the-art' and minimize the risks of design and safety issues due any adverse events reported.

The design input delineates the required specifications including the details of materials used, process additives, residues that can potentially be left and the dimensions for the sheath, retention features, material, composition, and amount for the lubricant, dressing materials, details of packaging materials which is related to safe handling and storage of the female condom. The design input also includes the required physical strength and elasticity of the barrier sheath and the other components in the female condoms are appropriately built in them. While selecting the materials, due consideration is given to potential presence of residual accelerators, nitrosamines, monomers of materials used, residue of solvents used, degradation products generated during shelf life of female condoms and such other chemical residues which could have impact on the safety and biocompatibility. These evaluations also include properties of the materials of construction of retention features, any process additives such as mould releasing agents, washing solvent residues, etc.

A method for determination of nitrosamines is available in ISO 29941.

When female condoms are made of natural rubber latex, the potential of latex allergy is also considered and the manufacturing operations appropriately planned and implemented to reduce the potential of latex allergy.

4.2.2 Barrier sheath

The barrier sheath or pouch is made of materials established to be safe and nontoxic for use in inserted condition in contact with vaginal mucosal membrane. ISO 25841 requires that they should not liberate any toxic chemicals or leave any toxic residues during storage and use. The pouch is usually of tubular shape with the insertion features and retention features either attached to the sheath by fusing or as a free component, by assembling process after the sheaths are manufactured. The female condom, in the assembled form, is evaluated for compliance with the requirements of barrier properties according to 4.4.1.

4.2.3 Product insertion feature and retention feature

The insertion feature and retention feature may be produced by the manufacturer of female condoms themselves or procured from approved vendors under a well-defined technical agreement. The technical agreement covers the details of the material of construction such as:

— those of elastomers and open cell or closed cell sponges and design of these devices, which are currently being used;

— the evaluations of compatibility of the materials used with the barrier sheath and the lubricant which form the other integral parts of the female condoms;

— conformance with the requirements of biocompatibility evaluations as per ISO 10993-1, ISO 10993-5, ISO 10993-10, ISO 10993-23, and in addition ISO 10993-3, if necessary, when materials known for negative effects in genotoxicity, carcinogenicity and reproductive toxicity are used in exceptional cases if, for some reason.

During design and manufacture of these components, adequate consideration is given to ensure that the geometry and design of these devices are fit for the purpose and they do not cause any injury to the vaginal mucosa and skin of penis during use.

4.2.4 Dressing materials

The dressing powders are used essentially for providing a smooth surface and for avoiding stickiness of the condom during storage and use. The dressing materials that are used are selected based on the physical and chemical compatibility with the components of female condoms and overall biocompatibility evaluation requirements of female condoms.

4.2.5 Lubricants

The female condoms contain lubricants which are chemically compatible with the other components of the female condoms and comply with requirements of biocompatibility evaluations. Since the surface area of female condoms is much larger than that of male condoms, the quantity of lubricant to cover the entire surface of female condoms is much higher. The material and grade of the material such as viscosity are important considerations that go in the selection of lubricant for female condoms. The quantity of lubricant used varies for each design of female condoms. The ability of the lubricant to migrate and cover the entire surface of the female condoms is also considered in the evaluation of the lubricants.

During the use of female condoms, the need for additional lubricants may become necessary. The additional lubricant may be supplied as companion sachet packs in a composite pack, by the manufacturer of female condoms. In some cases, the use of stand-alone personal lubricants is also recommended. The development of the design of female condoms includes the evaluation of compatibility of such additional lubricants with the female condoms before including or recommending them for use with the female condoms.

4.2.6 Biocompatibility

While designing the female condoms, the requirements of ISO 25841 for biocompatibility evaluation for the female condoms and their components such as barrier sheath, insertion features, dressing materials, lubricants, pigments and fragrances, if used, are considered and ensured that they are complied with.

4.2.7 Control of bioburden

The female condoms are nonsterile medical devices. However, since they come in contact with vaginal mucosa and outer skin of penis, in order to minimize the potential of infection, it is essential that they do not contain excessive microbial population and are free from pathogenic microbes such as *Staphylococcus aureus, Pseudomonas aeruginosa and Enterobacteriaceae*, including *Escherichia coli*. ISO 25841 recommends that the manufacturers control the total viable microbial counts and ensure the absence of specific pathogens as above. In order to achieve this, manufacturers consider the bioburden control aspects in the design and manufacturing stages. Some of the dressing materials such as starch can be a good medium for proliferation of microbes. The assembly of female condom sheath with the retention features is done usually by manual operation. Implementation of appropriate control measures enable controlling the bioburden potentially caused by manual operation. Additional details are given in Clause 6.

4.2.8 Packaging

The material and construction of individual containers are designed such that containers offer adequate protection against mechanical damage, oxidation, direct sunlight, and excessive humidity

(where applicable) to the female condom, which is packed in it. The composition and structure of laminates used for packing the female condoms in individual container ensure that the stability of the female condoms is maintained throughout the labelled shelf life, when stored at the prescribed storage conditions. Since the female condom is quite bulky in size and contains more quantity of lubricants, in comparison to male condom, the design of an individual container includes additional considerations to provide effective sealing to comply with the requirements of ISO 25841 with respect to visibly open seals and package seal integrity. The labelling requirements, according to ISO 25841, are also the factors which are considered in design and determination of the size of the individual containers appropriate to include the required labelling matter in legible form.

4.3 Design verification

The verification of the design performed in the prototype designs includes verification of physical and chemical properties, safety, biocompatibility evaluations, clinical performance evaluations and stability evaluations. The methods used for these verifications may involve specific instruments, as detailed in the data sheet to ensure conformance with the requirements as given in ISO 25841. The properties and attributes that are verified include verification of mechanical strength and elasticity, measured in terms of burst volume and burst pressure of the female condom design. The limits of burst volume and burst pressure are arrived at specifically for each design, based on the samples used for clinical studies which were proven to comply with the requirements of clinical investigations, as described in 4.4.2. Other parameters such as tensile properties may also be included in the design verification. It is also important to verify the physical properties of the retention features in terms of their dimensions, freedom from deformation of shape, hardness, stiffness (modulus), density and firmness of fixing of retention features, as applicable. Shelf-life estimation and stability evaluations are carried out as part of design verification. Adequacy of measures prescribed for control of bioburden as per ISO 25841 are also verified.

4.4 Design validation

4.4.1 Evaluation of barrier properties

The efficacy of the barrier properties of the film and the new design of female condom and if significant change(s) is made is established by evaluation of barrier properties as described in ISO 25841:2017, Annex H. Bacteriophage Phi- X174 is used as surrogate for evaluating the resistance to permeability of viruses and other microorganisms and spermatozoa for fulfilling the requirement of the contraceptive and STI prophylactic barrier properties. ISO 25841 provides for other test substances to be used, provided that such test substance is validated to be equivalent to the specified bacteriophage in simulating the permeability parameters.

4.4.2 Clinical (human use) investigations

ISO 25841 prescribes the following requirements for the validation of any new design of female condom and if significant change(s) is made:

a) clinical effectiveness study for pregnancy rate evaluation;

b) extrapolation from clinical effectiveness study of already approved female condom. If the design and specification of new female condom are sufficiently like those of a marketed device and that marketed device has a known pregnancy rate established from a clinical effectiveness study, then the manufacturer may refer to the estimated pregnancy rate of the marketed device instead of conducting a contraceptive effectiveness study on the new device. The requirements of selection of the control condoms are given in ISO 25841.

4.4.3 Stability studies and shelf-life claim

The shelf-life claim of the female condoms is validated by conducting stability studies according to ISO 25841, on female condoms that have been stored for the maximum validated period in unfoiled condition. The stability studies are conducted on samples from minimum three lots of fully assembled