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Copper-bearing contraceptive intrauterine devices — Requirements and tests

Dispositifs contraceptifs intra-utérins contenant du cuivre — Exigences et essais

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Foreword

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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 document 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).

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This document was prepared by Technical Committee ISO/TC 157, *Non-systemic contraceptives and STI barrier prophylactics,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 285, *Non-active surgical implants,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 7439:2015), which has been technically revised.

The main changes are as follows:

— the subclause on clinical performance has been revised (see 5.2);

— the movable collar has been added in the subclause on insertion instrument (see 6.3.4);

— requirements for packaging integrity have been added;

— the instructions for health care providers have been amended in accordance with the "Family planning: A global handbook for providers"[4];

— the requirement for stability in situ has been removed since there is no practical way of controlling it.

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

Although every foreign object in the uterus exhibits a certain contraceptive effect, the method by which copper-bearing contraceptive intrauterine devices (IUDs) function is by the continuous release of copper ions. This interferes with some enzymatic functions, immobilizes sperm cells and inhibits fertilization.

The IUD is a highly effective contraceptive device with a long history of safe use. It can be used for many years, with a prompt return of fertility upon removal.

IUDs do not prevent sexually transmitted infections and condom use is recommended for those at risk.

IUDs containing copper are regarded as single use sterile medical devices implanted in the uterus. These medical devices are inserted and removed by trained and competent health care providers.

Copper-bearing contraceptive intrauterine devices — Requirements and tests

1 Scope

This document specifies requirements and tests for single-use, copper-bearing contraceptive intrauterine devices (IUDs) and their insertion instruments.

It is not applicable to IUDs consisting only of a plastics body or whose primary purpose is to release progestogens or other medicinal products.

NOTE Some aspects of this document can be applicable to medicated intrauterine devices and IUDs not containing copper.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of 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 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14630:2012, *Non-active surgical implants — General requirements*

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

ISO 15223-1, *Medical devices — Symbols to be used with information to be supplied by the manufacturer — Part 1: General requirements*

ASTM D 3078, *Standard test method for determination of leaks in flexible packaging by bubble emission*

ASTM F 1929*standard test method for detecting seal leaks in porous medical packaging by dye penetration*

European Pharmacopoeia, (Ph. Eur.)[1)]

3 Terms and definitions

For the purposes of this document, the following terms and definitions 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/

3.1
contraceptive intrauterine device
IUD
copper-bearing device placed in the uterine cavity for the purpose of preventing pregnancy

1) European Directorate for the Quality of Medicines (EDQM) of the Council of Europe.

3.2
insertion instrument
instrument designed to place an IUD in the uterine cavity

3.3
thread
retrieval string attached to an IUD for the purposes of verifying the presence and facilitating the removal by a trained health care provider

Note 1 to entry: The thread is intended to lie in the cervical canal and the vagina when the body of the device is placed correctly in the uterine cavity.

3.4
viscoelastic property
property of an IUD enabling an approximate return to its initial configuration after deformation

3.5
active surface area
surface area of copper in the IUD that is intended to come into contact with uterine fluids

3.6
lot
quantity of IUDs produced during essentially the same time using the same process, same lots of raw materials, common equipment and which are sterilized at the same time

3.7
client
recipient or patient receiving a contraceptive product

3.8
unique device identifier
series of numeric or alphanumeric characters that is created through a globally accepted device identification and coding standard

Note 1 to entry: The unique identifier might include information on the lot or serial number and be able to be applied anywhere in the world. It allows the unambiguous identification of a specific medical device.

4 Quality verification

Copper bearing IUDs should be manufactured within an integrated quality management system conforming to ISO 13485.

NOTE For most countries and regions, this is a regulatory requirement.

For quality verification purposes, the sample size requirements and acceptance criteria specified in Annex A shall be used. These requirements are based on ISO 2859-1.

The sampling plans have been simplified to take into account typical industry lot sizes, the specific characteristics of IUDs and the nature of the manufacturing processes used to produce them. The sample sizes and acceptance criteria have been selected to provide an acceptable level of consumer protection taking into account the costs of sampling and testing. In addition to verification testing, it is strongly recommended that manufacturers conduct process validation and capability studies, and adopt statistical process control procedures such as the use of control charts to ensure acceptable product quality.

The sampling and acceptance criteria given in Annex A are intended to cover the following situations:

a) continuing production of lots within a stable manufacturing environment;

b) the assessment of isolated lots (e.g. fewer than 5), for example when purchasers wish to conduct confirmatory testing on a limited number of lots, when production is interrupted or intermittent, or for surveillance testing.

In addition, the rules for switching between normal and tightened inspection in ISO 2859-1 have been adopted to provide greater level of consumer protection should the quality of a manufacturing process deteriorate. These rules are applied as follows:

— Normal inspection – the specified sample sizes for normal inspection apply at the start of production. Normal inspection continues to apply unless two nonconforming lots are found in any sequence of 5 or fewer lots tested. If this occurs the number of samples used to assess the conformity for future lots shall be increased to those specified for tightened inspection.

— Tightened inspection – the specified sample sizes for tightened inspection shall apply until a sequence of 5 lots have been accepted. Following the acceptance of 5 sequential lots, the manufacturer may return to the sample sizes for normal inspection.

The switch to reduced inspection has not been adopted for the testing of copper bearing IUDs. Switching to smaller sample sizes is not considered acceptable given the potential for increased consumer risk because of the small sample sizes specified under normal inspection for many of the tests.

5 Intended clinical performance

5.1 General

ISO 14630:2012, Clause 4, shall apply.

ISO 14155 shall apply.

5.2 Clinical performance

5.2.1 General

An IUD shall meet the requirements specified in 5.2.2.to 5.2.9, based on a single-arm clinical study over a period of five years of user wear-time (the minimum intended lifetime of use). The manufacturer shall present these data in a final report of the clinical evaluation before releasing a modified or newly designed IUD onto the market.

NOTE 1 Guidance conducting a clinical study of Cu-IUDs is provided in ISO 11249[2].

The IUD and IUD insertion instrument shall be carefully designed to work together. The clinical study design shall ensure that the insertion instrument used in the study is the same (or very similar) instrument that is marketed either with or for the IUD.

NOTE 2 Clinical validation for minor changes that do not affect the safety and effectiveness of the insertion device might not be necessary. Significant changes that might affect the safety and effectiveness can require a new clinical validation according to ISO 11249.

5.2.2 Study duration

The clinical study duration shall be a minimum of five years, i.e. follow study subjects for a minimum of five years of user wear-time. The duration shall be as long as the proposed duration of use for the IUD labelling.

5.2.3 Study population

The clinical study population shall comprise women who are at risk for pregnancy, i.e. women who have regular unprotected heterosexual vaginal intercourse.

5.2.4 Sample size

5.2.3.1 The study sample size shall be sufficient to yield 10 000 woman-months of use in the first year of the clinical study.

5.2.3.2 The study sample size shall be sufficient to yield 200 women who fully complete a minimum of five years of wear-time. Longer follow-up is required if a longer wear-time is specified.

5.2.3.3 For IUDs with innovative designs, i.e. different shapes, surface features or metallic composition, that have not previously been subjected to a full clinical investigation, the study sample size shall be sufficient to yield 20 000 woman-months of use in the first year of the clinical study.

NOTE 1 This requirement applies to IUDs that are not equivalent to designs that have been subjected to clinical validation.

NOTE 2 The developer of a new IUD is responsible for checking whether the new IUD represents an innovative design that will be subject to the more stringent clinical study design requirements.

5.2.3.4 For IUDs with innovative designs, the study sample size shall be sufficient to yield 400 women who fully complete five years of wear-time.

To account for IUD expulsions and IUD discontinuation in a single-arm, 5-year clinical study, approximately 900 to 1 000 women should be enrolled. A statistical analysis should be undertaken to establish the study sample size and the total number of women to be enrolled.

5.2.5 Contraceptive performance

For the first year of the clinical study, the upper limit of the 95 % confidence level, two-sided confidence interval, for the one-year pregnancy rate computed using life table methods[3] shall be <2 %. A one-year pregnancy rate shall be calculated by the same methodology for each subsequent year of the study and shall meet the same performance target of <2 %.

NOTE For clinical contraceptive studies, pregnancy is the obvious outcome of interest, but there are other ways to analyse and present study results on effectiveness. Besides life-table analysis, some regulatory bodies require alternate analyses, e.g. the Pearl Index. Before initiating a clinical study, a study sponsor is expected to consult with the relevant regulatory body that will review the study results.

5.2.6 Expulsion rate

For the first year of the clinical study, the one-year expulsion rate computed by life table methods shall be <10 %. A one-year expulsion rate shall be calculated by the same methodology for each subsequent year of the study and meet the same performance target of upper limit of <10 %.

5.2.7 Discontinuation rate

For the first year of the clinical study, the one-year discontinuation rate computed by life table methods shall be <35 %. A one-year discontinuation rate shall be calculated by the same methodology for each subsequent year of the study and meet the same performance target of upper limit of <35 %.

5.2.8 Investigation report

A clinical investigation report on the clinical study shall be generated that provides all relevant clinical information from the study. See ISO 14155:2020, 8.4 and Annex D. At a minimum, the report shall present the following results:

a) Rates on the following:

— unintended pregnancies, specifying ectopic pregnancies;

— IUD expulsions;

— IUD removals due to bleeding;

— IUD removals due to pain;

— IUD removals due to pelvic inflammatory disease;

— IUD removals for other medical reasons;

— IUD removals for planned pregnancy;

— IUD removals for other personal reasons;

— IUD removals at the clinical investigator's choice; and

— loss to follow up.

b) Data on the following:

— discontinuation rate, including time between insertion and removal;

— effects on bleeding pattern;

— occurrence of uterine cervical perforation;

— return of fertility after IUD removal;

— outcome in the event of pregnancy with the IUD still in situ;

— other side effects;

— complications during IUD removal, e.g. severe pain, bleeding, broken IUD, broken retrieval thread.

For collecting data on pain, bleeding and other patient reported outcomes (PROs), it is recommended that study sponsors employ a validated PRO instrument, such as an eDiary, to improve ease-of-use, patient compliance and data accuracy. See also ISO 11249.

c) Information on each study subject:

— age, gravidity and parity of each study subject;

— timing of IUD insertion relative to the menstrual cycle, e.g. interval, postpartum, post-abortion;

— frequency of clinical visits during the follow-up period;

— training, experience and skill of the clinical investigator(s).

5.2.9 Labelling

All information and labelling relating to clinical performance data, shall be reviewed annually and updated as necessary. See Clause 12.

6 Design attributes

6.1 General

ISO 14630:2012, Clause 5, shall apply.

Thread and copper shall be integral parts of the IUD.