INTERNATIONAL STANDARD

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Second edition
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Copper-bearing contraceptive intrauterine devices — Requirements and tests

Dispositifs intra-utérins contenant du cuivre — Exigences, essais

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ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 7439 was prepared by Technical Committee ISO/TC 157, *Non-systemic contraceptives and STI barrier prophylactics*.

This second edition[1)] cancels and replaces the first edition (ISO 7439:2002), of which it constitutes a minor revision.

1) ISO 7439:2002 was incorrectly given as being the “second” edition, but as it replaced a Technical Report, ISO/TR 7439:1981, as such it was the *first* edition as an International Standard.

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. These contribute to the high effectiveness of the contraception.

The effectiveness of copper-bearing IUDs is many times greater than that of a simple plastics body.

Contraceptive IUDs containing copper are regarded as medical devices incorporating a substance with an ancillary action and are subject to the European Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.

Contraceptive IUDs whose primary purpose is to release progestogens are regulated as medicinal products and are subject to the European Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products. The relevant essential requirements of Annex I to Directive 93/42/EEC apply as far as safety and performance-related device features are concerned. It is advisable that significant changes in the design of the IUD, insertion device, specification or insertion technique be validated.

Copper-bearing contraceptive intrauterine devices — Requirements and tests

1 Scope

This International Standard 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.

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

2 Normative references

The following referenced documents are indispensable for the application 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 14155-1, *Clinical investigation of medical devices for human subjects — Part 1: General requirements*

ISO 14630:2008, *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 medical device labels, labelling and information to be supplied — Part 1: General requirements*

European Pharmacopoeia (Ph. Eur.) [2)]

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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

2) 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
attachment to an IUD for the purposes of verifying the presence and enabling the removal of the IUD

NOTE 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
visco-elastic 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

4 Intended performance

4.1 General

ISO 14630:2008, Clause 4, shall apply.

4.2 Clinical performance

An IUD shall meet the following requirements for a period of five years (the minimum intended lifetime of use):

— the upper limit of the 95 % confidence level, two-sided confidence interval for the one-year pregnancy rate computed using life table methods shall be $\leqslant$ 2 %;

— one-year expulsion rates computed using life table methods shall be $\leqslant$ 10 %;

— one-year discontinuation rates computed using life table methods shall be $\leqslant$ 35 %.

5 Design attributes

5.1 General

ISO 14630:2008, Clause 5, shall apply.

Thread and copper shall be integral parts of the IUD.

5.2 Shape

When tested by visual and tactile inspection, an IUD shall have a form fitting the uterine cavity and designed in such a way as to minimize the risk of perforation and subsequent bowel obstruction. The IUD and insertion instruments shall not exhibit sharp edges.

The design of the IUD shall be such that no excessive forces are required for insertion and removal.

5.3 Dimensions

5.3.1 IUD

The nominal length of an IUD shall be $\leqslant$ 36,2 mm; the nominal width of an IUD shall be $\leqslant$ 32,3 mm.

When determined as specified in 7.2.1, the dimensions shall be consistent with the specifications as given by the manufacturer within tolerances of $\pm$ 5 %.

5.3.2 Copper components

The nominal active surface area of copper shall be at least 200 mm^2 but shall not be larger than 380 mm^2. If copper wire is used, the nominal diameter of the copper wire shall be at least 0,25 mm.

The diameter shall be consistent with the specifications given by the manufacturer within tolerances of $\pm$ 5 % and the active surface area within tolerances of $\pm$ 10 %.

5.3.3 Thread

When determined in accordance with 7.2.2, the length of the thread shall be not less than 100 mm.

5.3.4 Insertion instrument

The maximum nominal outer width of that part of an insertion instrument intended to come into contact with the cervical canal shall not be greater than 5 mm.

The dimensions shall be consistent with the specifications given by the manufacturer within tolerances of $\pm$ 5 %.

5.4 Tensile force

When tested in accordance with 7.3, the IUD, including the thread, shall withstand a tensile force as given in Table 1.

Table 1 — Tensile force of IUDs

IUD type	Tensile force N
T-shaped devices	9,5
All other devices	12

5.5 Stability

5.5.1 Shelf-life stability

The IUD shall meet any performance specification given by the manufacturer based on *in vitro* studies for the complete duration of the declared shelf life.

5.5.2 *In situ* stability

During the length of the intended period of use, the frame, together with copper components, shall retain structural integrity and the entire IUD shall withstand the tensile force in accordance with 5.4.

5.6 Visco-elastic property

When tested in accordance with 7.4, the recovery of any part of the IUD from its original design position shall be such that the residual deformation does not exceed 5 mm.

5.7 *In situ* detection

All parts of the IUD frame shall be detectable by X-ray examination. If barium sulphate is used in the plastics components as the opaque material, its content shall range from 15 % (*w/w*) to 25 % (*w/w*), when tested in accordance with 7.5.

6 Materials

ISO 14630:2008, Clause 6, shall apply.

The plastics body, including the substance conferring radio-opacity, shall be visco-elastic, biocompatible and non-absorbable.

The thread shall be monofilament, biocompatible and non-absorbable.

The purity of the copper shall be at least 99,9 %, which shall be certified.

7 Design evaluation

7.1 General

14630:2008, 7.1, shall apply.

7.2 Determination of dimensions

7.2.1 For determining the dimensions of the IUD and the outer diameter of the insertion instrument, a method that does not alter the shape, e.g. a contour analyser or any other instrument providing similar accurate results, shall be used.

7.2.2 For determining the length of the thread, a ruler or any other instrument providing similar accurate results shall be used.

7.2.3 The active surface area shall be computed using mathematical formulas.

7.3 Determination of tensile force

7.3.1 Principle

The IUD, including the thread, is stretched until breakage of the IUD or detachment or breakage of the thread occurs. The force required to cause breakage is measured.

7.3.2 Apparatus

Tensile testing machine capable of a substantially constant rate of traverse and complying with the following:

a) a force range of 0 N to 100 N;

b) a separation speed of (3,3 ± 0,3) mm/s or (200 ± 20) mm/min;

c) automatic recording of force applied during testing; a chart recorder may be used.

7.3.3 Procedure

The test method shall be designed in such a way that the potentially weakest part of the IUD is exposed to the tensile force.

Condition the IUD at a temperature of (23 ± 2) °C and relative humidity of (50 ± 5) % for at least 24 h. Place each IUD into the tensile testing machine according to the manufacturer's instructions. If no instructions are supplied by the manufacturer, place the upper part of the IUD in the upper clamp with thread(s) placed in the lower clamp at a distance of 5 cm from its point of attachment to the IUD. Then apply force to stretch the IUD until either it or the thread breaks or detaches. Measure and record the force at break or detachment.

7.3.4 Test report

The test report shall include the following:

a) identification of the sample;

b) number of IUDs tested;

c) breaking force, in newtons, of each IUD;

d) position of the break;

e) date of testing.

7.4 Test of visco-elastic property (memory test)

7.4.1 Principle

The visco-elastic property of the IUDs is tested by determining the recovery after acute flexion.

7.4.2 Procedure

The IUD is conditioned at a temperature of (23 ± 2) °C and relative humidity of (50 ± 5) % for at least 24 h.

Depending on whether or not the IUD is to be deformed prior to insertion, the test shall be performed as follows.

a) **IUD to be deformed prior to insertion**

The position of both arms, or those parts of the IUD that will be subjected to folding either before insertion or when inserting the IUD, shall be determined in relation to the rest of the IUD. The arms (or parts) of the IUD are to be folded according to the manufacturer's instructions for application. They shall remain in this folded position for 5 min and then be allowed to recover their shape under zero load for 1 min.

NOTE T-shaped devices are usually inserted into a tube with an inner diameter of 3 mm to 10 mm.

b) **IUD not to be deformed prior to insertion**

The entire IUD shall be inserted into a tube with an inner diameter of (10 ± 0,1) mm for a period of 5 min and then removed and allowed to recover its shape under zero load for 1 min.

Determine the position of the arms or parts of the IUD that were subjected to folding.

7.4.3 Test report

The test report shall include the following:

a) identification of the sample;

b) number of IUDs tested;

c) for each IUD, the displacement of any parts from their original position;

d) date of testing.

7.5 Determination of barium sulphate content and identification of barium and sulphate

7.5.1 Ash content test

Ash content shall be determined using the European Pharmacopoeia sulphated ash method, but omitting the use of sulphuric acid.

7.5.2 Identity test

Identification tests A and B shall be performed in accordance with the monograph for barium sulphate (sulphate and barium) on the ash (from the ash content test) given as the current European Pharmacopoeia method.

7.6 Pre-clinical evaluation

A risk analysis shall be performed according to ISO 14971.

The biological safety shall be evaluated in accordance with the principles given in ISO 10993-1, according to which an IUD is classified as a medical device in contact with mucosal membranes, and the following supplementary tests shall be considered:

— chronic toxicity studies;

— carcinogenic studies;

— reproductive developmental toxicity studies.

7.7 Clinical evaluation

7.7.1 Before releasing modified or newly designed IUDs onto the market, the manufacturer shall present a clinical evaluation in accordance with the following.

Contraceptive efficacy rates shall be determined in a randomized controlled equivalence or non-inferiority trial using TCu380A, if possible, as the control device. If not, another IUD with a well-established pregnancy rate shall be used. Appropriate sample sizes shall be used to ensure that the pregnancy rate criterion specified in 4.2 can be met. Any trial shall include at least 20 000 woman months for the device under test.

Compliance with this International Standard can be demonstrated by conducting a randomized study in which an average of 720 women use the test device in the first year of the study and an average of 360 women in a control arm use the TCu380A device, if possible. If not, another IUD with a well-established pregnancy rate shall be used.

NOTE 1 A study with an average of 720 women followed during the first year of use and a true pregnancy rate of 1 % would have an approximate 95 % level, two-sided confidence interval for the first year pregnancy rate of 0,4 % to 2,0 %. Depending on the attrition rate in the study cohort, this could be achieved by enrolling between 900 and 1 000 women.

The control arm using TCu380A shall be included in the trial to confirm that no bias is introduced due to the study methodology and/or the population using the index device. This can be demonstrated if an average of 360 women are followed during the first year of use.

NOTE 2 Assuming a true pregnancy rate of 1 % for TCu380A, the approximate 95 % level, two-sided confidence interval for the first year pregnancy rate would be 0,2 % to 2,7 %. Depending on the attrition rate in the study cohort, this could be achieved by enrolling between 450 and 500 women. Hence the upper limit of the 95 %, two-sided confidence interval for the TCu380A ought not to be greater than 2,7 %.

NOTE 3 A randomized controlled study designed as an equivalence trial with an average number of 720 and 360 women in each arm would declare as equivalent two devices with true pregnancy rates of 1 % if the difference in observed pregnancy rates was $\leqslant$ 2,1 %. Therefore, a study of this size will have very limited significance.

7.7.2 The clinical evaluation shall be performed in accordance with ISO 14155-1.

7.7.3 As a result of the clinical evaluation, the following rates shall be obtained:

— unintended pregnancies, specifying ectopic pregnancies;

— expulsions;

— removals due to bleeding;

— removals due to pain;

— removals due to pelvic inflammatory disease;

— removals for other medical reasons;

— removals for planned pregnancy;

— removals for other personal reasons;

— removals at the clinical investigator's choice;

— loss to follow up.

7.7.4 Data on the following parameters shall be collected:

— continuation rate;

— effects on bleeding pattern;

— occurrence of uterine cervical perforation;

— return of fertility;

— in case a pregnancy occurs with an IUD *in situ*, the outcome of this pregnancy;

— other side effects;

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

7.7.5 Following the removal of an IUD, the following data shall be collected for a representative sample:

— amount of copper released;

— tensile force;

— structural integrity.

7.7.6 The following information on the procedure of the clinical evaluation shall be given:

— age, gravidity and parity of the women;

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

— clinical follow-up frequency;

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

8 Manufacturing and inspection

ISO 14630:2008, Clause 8, shall apply.

9 Sterilization

An IUD shall be supplied sterile.

ISO 14630:2008, Clause 9, shall apply.

10 Packaging

ISO 14630:2008, Clause 10, shall apply.

11 Information to be supplied by the manufacturer

11.1 General

ISO 14630:2008, 11.1 and 11.2, shall apply.

These requirements may be met by the use of appropriate symbols as given in ISO 15223-1.

11.2 Labelling of the primary container

The following information shall be given on the primary container:

— name or trade name and address of the manufacturer;

— the word “STERILE”;

— method of sterilization;

— batch code;

— expiry date;

— insert before date;

— the words “For single use only”, or equivalent, or the appropriate graphical symbol in accordance with ISO 15223-1;

— the maximum lifetime *in situ.*

11.3 Labelling of the secondary container

The following information shall be given on the secondary container:

— name or trade name and address of the manufacturer;

— batch code;

— expiry date;

— the words “For single use only” or equivalent.

11.4 Instructions for use

The following information shall be given to the medical professional in the instructions for use:

— international trade name;

— description of the design, dimensions and composition of the IUD;

— description of the intended use;

— statement that the IUD is sterile and for single use only;

— the timing of insertion, such as interval insertion, immediate post-abortion or post-partum insertion or postcoital insertion;

— description of the insertion procedure, which shall include illustrations;

— maximum time the IUD is allowed to be in the insertion instrument;

— maximum time *in situ*;

— description of the removal procedure and actions to be taken in case of difficulties during removal;

— absolute and relative contraindications[3)];

— warnings and precautions for use and specification of medical examinations to be performed prior to and during the use of the IUD; reasons for removal of the IUD;

— description of possible interactions with medication and other forms of treatment or investigation, such as diagnostic or therapeutic radiation;

— specification on what to do in case of an intrauterine or ectopic pregnancy with an IUD *in situ*; the risks involved where a pregnancy exists in the presence of an IUD;

— undesirable effects of the product, including their frequency and timing;

— description of the mode of action;

— incompatibilities;

— shelf life;

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3) Contraindications are considered to be absolute when the device is not to be used. Contraindications are considered to be relative when their presence permits use after a risk/benefit analysis.

— special precautions for storage;

— nature and contents of container;

— instructions for use, whereby it is mentioned that the medical professional should inform the woman about the risks and benefits of IUDs, and advice about periodical checks on the presence of the IUD and clinical signs and symptoms in the case of which the woman should contact the medical professional;

— name and address of the manufacturer;

— (in Europe) CE number according to Reference [2];

— date of first authorization/renewal of authorization;

— date of revision.

11.5 Information intended for the woman

The following information shall be given:

— the design, dimensions and composition of the IUD;

— the mode of action and possible effects on the menstrual cycle;

— contraindications and special precautions;

— any possible adverse reaction with concurrent medication;

— possible interactions with other treatments;

— the insertion and removal procedures;

— advisability of self-examination to verify the presence of the IUD;

— the procedure for periodically checking the presence of the IUD;

— a list of those related relevant clinical signs and symptoms which should prompt the woman to contact a physician;

— recommended maximum *in situ* time;

— possible complications and a description of clinical signs and symptoms in which case the woman should contact a physician;

— name and address of the manufacturer;

— date of last revision of the package insert.

Bibliography

[1] EN 12011, *Instrumentation to be used in association with non-active surgical implants — General requirements*

[2] EU Directive 93/42/EEC, *Medical devices*

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