Annex 10

WHO/UNFPA technical specification for TCu380A intrauterine device

Contents

Abbreviations

ABS	acrylonitrile-butadiene-styrene
AQL	acceptance quality limit
cm	centimetre
g	gram
GMP	good management practices
HDPE	high-density polyethylene
Hg	mercury
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISO	International Organization for Standardization
IUD	intrauterine device
kGy	kilogray
kJ	kilojoule
kPa	kilopascal
LDPE	low-density polyethylene
mm	millimetre
MPa	megapascal
N	newton
NDA	new drug application
OFE	oxygen-free electronic
PP	polypropylene
ppm	parts per million
RH	relative humidity
SAL	sterility assurance level
UNFPA	United Nations Population Fund
UNS	unified numbering system
USP	United States Pharmacopeia
WHO	World Health Organization

1. Introduction

This annex contains the World Health Organization (WHO) and United Nations Population Fund (UNFPA) technical specification for TCu380A intrauterine device (IUD), which is suitable for bulk procurement of the TCu380A IUD for use in public sector programmes for family planning.

The WHO/UNFPA technical specification for TCu380A IUD covers the specific TCu380A IUD design and differentiates it from other generic copper-bearing IUDs. It also includes requirements for manufacturers for each of the individual components. A specification is a detailed and unambiguous statement of the requirements and describes the general design, performance, labelling and packaging requirements for the product and the methods of verification. A specification is part of the supply contract and will generally be attached to the bidding documents and forms.

The WHO/UNFPA technical specification for TCu380A IUD is based on the requirements for copper-bearing IUDs defined by the International Organization for Standardization (ISO) in ISO 7439:[1] Copper-bearing contraceptive intrauterine devices – Requirements and tests (1). This standard specifies the generic requirements for copper-bearing IUDs and the test methods that are used to assess conformance with these requirements. Specific requirements for the TCu380A IUD are based on the Population Council New Drug Application (NDA) 18-680 (Copper T model TCu380A) (*2*). The standard ISO 7439 is referred to generically throughout this specification; unless otherwise specified, it should be assumed that the most recent edition of this internationally agreed standard applies.

The requirements in this specification are divided into the following three sections:

- **General requirements** specify the safety of constituent materials and other characteristics, such as shelf-life, materials, product and component dimensions, storage, biocompatibility, sterility and method of sterilization. These requirements are normally assessed by material and process validation, including testing, where appropriate, by the manufacturer. Revalidation is required following any significant change to the sourcing of raw materials or changes in the manufacturing processes. The general requirements detailed in the *TCu380A intrauterine contraceptive device: WHO/UNFPA technical specification and prequalification guidance 2016* (*3*) may not be changed by the purchaser. Conformance with the general

[1] When references to standards are undated the most recent edition of the standard applies.

requirements is verified during prequalification. The prequalification process aims to ensure that characteristics of the product do not change on a lot-by-lot basis.

- **Performance requirements** specify the essential performance attributes of the TCu380A IUD, established in accordance with ISO 7439 and the Population Council NDA. These must be verified on a lot-by-lot basis by the manufacturer and may be verified by the purchaser on a lot-by-lot basis. Performance requirements detailed in the *WHO/UNFPA technical specification and prequalification guidance 2016* (*3*) may not be changed.
- **Packaging and labelling requirements** are detailed in the *WHO/UNFPA technical specification and prequalification guidance 2016* (*3*) and may not be changed. Continuous film packaging combined with terminal radiation is preferred, as it reduces the risk of tarnishing. Additional labelling may be specified based on programmatic needs.

The WHO/UNFPA technical specification is based on:

- international standard ISO 7439 (*1*);
- Population Council NDA 18-680 (Copper T model TCu380A intrauterine contraceptive) (*2*);
- a literature review of the available evidence;
- the recommendations of the WHO/UNFPA IUD Technical Review Committee (November 2006, August 2008 and September 2013);
- feedback from participants attending the WHO/UNFPA workshops to introduce the TCu380A IUD specification, prequalification and procurement procedures, conducted in Bangkok, Thailand, in January 2010 and New Delhi, India, in February 2014.

Where appropriate, reference is made to the current edition and corrigenda of the published international standard ISO 7439: Copper-bearing contraceptive intrauterine devices – Requirements and tests (*1*).

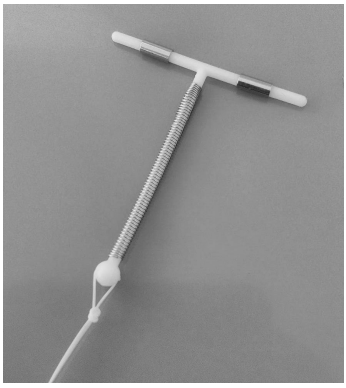
The WHO/UNFPA technical specification, if used in conjunction with the WHO/UNFPA Prequalification Programme and procurement procedure, will ensure that a quality-assured product is purchased and distributed to the end user.

The TCu380A IUD consists of a T-shaped frame made from low-density polyethylene with barium sulfate added for X-ray opacity (Fig. 1), with a plastic ball at the bottom of the vertical stem to guard against cervical penetration. The IUD has solid copper collars on each of its two horizontal arms. Each of these collars has a surface area of 35 square millimetres (mm^2). Copper wire with a surface area of 310 mm^2 is wound tightly around the vertical stem giving a total

surface area of 380 mm² of copper, as indicated in the name of the device. A pigmented polyethylene filament is tied in a knot through a small hole in the ball to provide two equal-length threads as a means to locate and remove the device. The device is packed in an individual pouch and subjected to post-packaging sterilization.

Tarnishing is a natural phenomenon for copper and does not affect the performance of the IUD. However, significant tarnishing of copper during storage may not be aesthetically acceptable. The use of continuous film packaging, which is suitable for gamma radiation sterilization, helps to reduce the problem of tarnishing.

Fig. 1
TCu380A IUD



In order to insert the device into the uterus, an insertion tube is used. The insertion tube keeps the TCu380A IUD correctly positioned within the uterus while the insertion rod is removed. The movable plastic flange is positioned on the insertion tube to control the depth of insertion and to locate the IUD correctly within the uterus during insertion.

Other devices to assist the process of insertion may also be provided, such as an arm-folding device, a uterine sound, sterile gloves or sterile swabs. When considering the design and choice of materials for these components, manufacturers should take into account the function of the devices, the type and duration of exposure to the body and the effect of sterilization.

Purchasers should assess the functionality, safety and effectiveness of any assist devices, including their potential effect on the IUD prior to purchase.

For IUDs specifically manufactured and labelled for postpartum insertion, deviations from the specifications regarding length of string and dimensions of the inserter are permitted if they can be clinically justified.

Copper-bearing IUDs are classified under European Medical Device Directive 93/42/EEC (as amended) as Class III medical devices with ancillary medicinal substances (*4*). The regulation of medical devices in Europe has been in transition with Medical Device Regulation EU 2017/745 (*5*), which came fully into force on 26 May 2020. The clinical studies detailed in the technical basis paper have all been conducted using the TCu380A IUD complying with the Population Council specification submitted in NDA 18-680, which requires a minimum copper purity of 99.99%. These studies have demonstrated that the TCu380A IUD based on this specification is both effective and safe.

2. Glossary

acceptance number. The highest number of nonconforming units (failures) allowed in a specific test from a selected sample.

acceptance quality limit (AQL). The quality level that is the worst tolerable process average when a continuing series of lots is submitted for acceptance sampling (ISO 2859-1).

Note: Manufacturers should be consistently achieving a process average that is better than the AQL.

batch. A term sometimes used in place of "lot" (see definition of "lot"). WHO recommends that the term "lot" be used when referring to medical devices. "Batch" can also refer to a quantity of individual raw materials.

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

CE mark. On medical product packaging, a mark certifying that the product conforms to the essential requirements of European Medical Device Directive 93/42/EEC.

critical defect. A defect that might affect the safety, acceptability or effectiveness of the product is classified as a critical defect, causing the device to be rejected.

expiry date. In the context of IUD manufacture, the expiry date is the date after which raw materials, components, and so on, are no longer considered acceptable for manufacturing IUDs.

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

insert before date (referred to in previous editions of the specification as "latest insertion date"). The date after which the device should not be inserted into the

uterus. (Occasionally, the term "expiry date" is used, but this can be confused with the latest date by which the device has to be removed from the uterus. The use of "expiry date" is therefore discouraged in this context.)

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

lot. A quantity of raw materials, components or IUDs made at essentially the same time and having a single lot identification code or number. Clear lot identification and recording are required to permit effective product recall in the event of a quality problem with the device. The definition of a lot of manufactured IUDs is given in section 3 on general requirements.

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

non-critical defect. A defect that might affect the acceptability of the product, causing the device to be rejected at the time of insertion, but is not expected to affect the safety or effectiveness of the device.

package. The film–film or film–Tyvek peel pouch in which the IUD is sealed after manufacture and sterilization.

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

process average. The percentage of nonconforming IUDs over a defined time period or quantity of production. It is calculated for each requirement detailed in the WHO/UNFPA TCu380A IUD technical specification by dividing the number of nonconforming IUDs by the total number of IUDs tested. Ideally, the process average for a specific attribute should not be greater than half the specified AQL.

random sample. A sample of IUDs drawn randomly from a lot for testing purposes.

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

shelf-life. The period of time after manufacture that the product is considered suitable for insertion, stated as the insert before date (previously, latest insertion date) on the pack.

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

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

summary of technical information. New document format introduced to replace the product dossier and site master file.

unified numbering system (UNS). An alloy designation of the National Bureau of Standards.

3. General requirements

The general requirements specified in this section shall not change from lot to lot. Conformance with these requirements is assessed during prequalification and also in case of doubts by the purchaser as to whether or not the product complies with the specification. Conformance may need to be assessed if any significant changes are made in the selection and sourcing of materials or the manufacturing procedures. As per prequalification requirements, manufacturers shall inform UNFPA of any changes that impact conformance with general requirements. The general requirements are set out in Table. 1, classified by category.

Table. 1
General requirements (to be evaluated during prequalification)

Requirements by category	Specifications
1.1 Lot definition	
Requirement	A lot is a homogeneous collection of IUDs made under essentially identical manufacturing conditions using the same lots of raw materials: low-density polyethylene (LDPE) compound, high-density polyethylene (HDPE) compound for thread, copper for wire and collars, and individual pouches and individual pouch material that are subjected to sterilization in the same sterilization cycle and assigned a unique number before release. Clear lot identification and recording are required to permit effective product recall in the event of a quality problem with the device.
1.2 Date of manufacture	
Date of manufacture requirement	The date of manufacture of a lot is the month and year in which the IUDs were sealed in the primary package for terminal sterilization. Sterilization shall be conducted in accordance with part 1.5 of this table.

Table 1 *continued*

Requirements by category	Specifications
1.3 Materials	
T frame requirements	The T frame shall be made from LDPE, free of stabilizers, having a minimum tensile strength of 13 megapascals (MPa) (ASTM D638 and ISO 527-2), using a crosshead speed of 50 mm/min and a type 1 specimen bar) and a 2% secant flexural modulus in the range 133.5 MPa to 180.6 MPa (ASTM D790). The LDPE shall be blended with 15% to 25% precipitated barium sulfate USP (United States Pharmacopeia) with a particle size of 95% less than 10 micron. The barium sulfate content of the frame material shall be determined according to the relevant clause of ISO 7439. See also the biocompatibility requirements for compounded polymer, below.
Copper wire requirements	The wire shall be made from oxygen-free electronic (OFE) 99.99% pure copper meeting the National Bureau of Standards designation UNS C10100. There shall be no coating on the wire.
Copper collars requirements	The copper collars shall be made from half-hard temper, seamless copper tube made from OFE 99.99% pure copper meeting the National Bureau of Standards designation UNS C10100. There shall be no coating on the collars.
Thread requirements	The thread shall be a monofilament made from HDPE, free of stabilizers, with sufficient tensile strength to meet the specified thread breaking force requirement greater than 9.5 newtons. A material with a minimum tensile strength (ASTM D638 and ISO 527-2) of 28 MPa is recommended. The thread polymer shall be compounded with 0.4% up to 1.0% by weight rutile titanium dioxide (USP and European Pharmacopeia). See also the biocompatibility requirements for compounded polymer, below.
Insertion tube requirements	The insertion tube shall be made from HDPE food contact grade.

Table 1 *continued*

Requirements by category	Specifications
Insertion rod requirements	The rod shall be made from food contact grade radiation-stable acrylonitrile-butadiene-styrene (ABS) polymer or food contact grade radiation-stabilized polypropylene (PP). Optionally, the insertion rod may be pigmented.
Positioning flange requirements	The flange shall be made from a polymer with adequate radiation stability to permit sterilization without any significant change in properties, including flange displacement force. Optionally, the flange may be pigmented.
Biocompatibility requirements	The compounded T frame polymer (LDPE plus barium sulfate) and compounded thread, as an assembly or separately, shall be evaluated for biological safety in accordance with ISO 10993-1 requirements for devices principally contacting tissue and tissue fluid contact devices intended for permanent contact. Specifically, the following is required: • evaluation for genotoxicity according to ISO 10993-3; • evaluation for cytotoxicity according to ISO 10993-5; • evaluation for local effects after implantation according to ISO 10993-6; • evaluation for irritation and delayed-type hypersensitivity according to ISO 10993-10; • evaluation for subacute and subchronic toxicity according to ISO 10993-11. Testing must be performed by a laboratory that is accredited to ISO 17025, with IUD testing included in the scope of accreditation. For a specific material, it is only necessary to carry out the assessment of biological safety once. The evaluation shall be repeated if there is a significant change to the materials; for example, if the grade or supplier is changed.

Table 1 *continued*

Requirements by category	Specifications
	Where a manufacturer sources components or materials from another IUD manufacturer, it is not necessary to conduct a further biocompatibility assessment on those components or materials, provided that the manufacturer supplying the components or materials has conducted a biological safety evaluation and has made the results of that evaluation available to the manufacturer using the components or materials. The manufacturer purchasing the components or materials shall maintain a technical file containing the biocompatibility information provided with the components or materials. Manufacturers may continue to use their current grades of LDPE and HDPE if these are consistent with the Population Council specification without conducting the biocompatibility evaluation on the T frame compound with barium sulfate or thread compound with titanium dioxide. It is required that all biological safety tests in accordance with ISO 10993 parts 1, 3, 5, 6, 10 and 11 be conducted by laboratories accredited for these tests. Detailed requirements are provided in section 7.7.
Material procurement and control requirements	Manufacturers are responsible for ensuring all operations, including those undertaken by subcontractors, such as material storage, compounding of the frame and thread materials and moulding, are done to acceptable standards, as specified below. There should be adequate control procedures and documentation to ensure and demonstrate conformance in accordance with ISO 13485. These procedures should ensure that batches of compounded materials (T frame, thread materials) and moulding and extrusion of the components are not contaminated by any extraneous impurities during processing operations. Where lubricants are used in moulding and extrusion, the grades shall be food grade or suitable for medical device manufacture. Materials and components should be stored in a manner in which they are protected from light and high humidity. The storage conditions shall ensure conformance with bioburden levels specified for the product.

Table 1 *continued*

Requirements by category	Specifications
	If appropriate, the copper components or other components should be cleaned prior to assembly. Manufacturers shall introduce procedures to monitor and control the degree of tarnish and rough edges on the copper components. The maximum storage period before retesting of the raw material is required for the frame polymer and the thread is three years from the date of manufacture when stored at temperatures below 30 °C and two years when stored at temperatures between 30 °C and 35 °C. Provided the breaking force of the frame material exceeds 13 MPa (which may be determined by testing moulded frames) and the breaking force of the thread exceeds 9.5 newtons (N), then the materials may be used for a further three years when stored at temperatures below 30 °C and two years when stored at temperatures between 30 °C and 35 °C. Every new lot of compounded frame material (LDPE plus barium sulfate) and thread material (HDPE plus titanium dioxide) shall be subjected to in vitro cytotoxicity testing in accordance with ISO 10993-5: Biological evaluation of medical devices. For tests for in vitro cytotoxicity, see section 7.7. The cytotoxic response shall not be worse than that recorded for the compounded material when originally evaluated for biological safety according to the requirements of ISO 10993-1.
Packaging	IUDs shall be packed in film–film pouches for better protection and to improve confirmation of package integrity, unless sterilization is by ethylene oxide.
Material processing requirement	The recycling of injection moulded reclaim material for the T frame and the thread is not permitted.
1.4 Shelf-life, maximum in situ time and stability	
Stability studies requirements	Claims about shelf-life shall be supported by real-time stability data collected in accordance with Appendix 3. Accelerated ageing stability studies may be submitted pending the completion of real-time studies. Guidance on conducting stability studies is given in Appendix 3, on guidance for stability studies.

Table 1 *continued*

Requirements by category	Specifications
Insert before date requirements	The insert before date is the maximum permitted shelf-life for storage of the device prior to insertion and is normally five years. By agreement with the purchaser, the shelf-life may be extended to seven years subject to satisfactory real-time stability data being available and reviewed for the full seven years for storage in climatic zone IVB, 30 °C/75% relative humidity (RH). The stability data shall include package integrity testing substantiating maintenance of sterility.
Maximum in situ time	Based on efficacy and safety evidence, the maximum in situ time is 12 years.
1.5 Bioburden control and terminal sterilization	
Sterilization and method requirements	The TCu380A IUD shall be supplied sterile in a sealed primary pack (pouch) together with the insertion tube, the insertion rod and the positioning flange. Sterilization shall be by radiation according to ISO 11137 series, or by ethylene oxide according to ISO 11135 series, and standards normatively referenced therein. Radiation sterilization is preferred, to allow the use of continuous polymer film packaging materials. The sterilization shall be completed within 30 days of sealing the finished device in the pouch.
Sterility assurance level requirements	The sterilization assurance level shall be 1×10^{-6}.
Residual ethylene oxide levels requirements	If ethylene oxide sterilization is used, then residual ethylene oxide levels shall not exceed 10 parts per million (ppm), and ethylene chlorohydrin levels shall not exceed 20 ppm, on any individual sample when measured using a method that complies with the requirements of ISO 10993-7. Average residual levels across all samples tested shall not exceed 5 ppm for ethylene oxide and 10 ppm for ethylene chlorohydrin. Guidance on bioburden control and terminal sterilization is given in Appendix 2.

Table 1 *continued*

Requirements by category	Specifications
1.6 Component specifications	
T frame	Length of horizontal arms (total length of both arms): (32 ± 0.5) mm. Length of vertical stem: (36 ± 0.5) mm. Diameter of horizontal arm: (1.6 ± 0.1) mm. Diameter of vertical stem: (1.5 ± 0.1) mm. Optionally, a hole for anchoring an end of the copper wire may be provided. The maximum diameter of the hole shall be 0.55 mm. The T piece ball (at the end of the vertical stem) shall have a diameter of (3.0 ± 0.7) mm. The junction between the ball and the vertical stem shall preferably be radiused. The T piece ball (at the end of the vertical stem) shall have a hole of maximum diameter 0.80 mm for securing the thread. The hole may be tapered or dumb-bell shaped. The junctions between the horizontal arms and the vertical stem may be radiused to prevent stress concentrations. If the junction is radiused, the radius shall be between 0.25 mm and 0.40 mm. Manufacturers shall confirm that introducing the radius does not lead to an increase in crush damage at the junction when the T is deformed as it is loaded into the insertion tube. This can be achieved by comparing the strength of radiused and non-radiused T frames after loading in the insertion tube. Microscopic examination should be used alongside strength testing to monitor the extent of any damage. A drawing of the T frame is included in Appendix 1.
Copper wire	The diameter of the wire shall be (0.255 ± 0.005) mm (30 AWG, 33 ISWG).
Copper collars	The internal diameter shall be (1.68 ± 0.025) mm and external diameter (2.2 ± 0.025) mm. The collars shall be (5 ± 0.15) mm in length. The collars shall be deburred, polished and free from sharp edges; for example, by barrel tumbling. A drawing of the copper collar is included in Appendix 1.

Table 1 *continued*

Requirements by category	Specifications
Thread	The thread diameter shall be (0.25 ± 0.05) mm.
Insertion tube	The length of the insertion tube shall be (206 ± 2) mm. The internal diameter of the insertion tube shall be (3.7 + 0.2/−0.1) mm. This should be determined using a plug gauge. The outside diameter of the insertion tube shall be (4.4 + 0.2/−0.1) mm.
Insertion rod	The length of the insertion rod shall be (190 ± 5) mm from handle brace to tip. The insertion rod shall be a snug fit but slide smoothly within the insertion tube and shall not trap the thread. It is recommended that the rod have a thickened section, spline or ridge to help retain the rod within the insertion tube. The diameter of the insertion rod at tip shall be (2.6 ± 0.2) mm. The rod diameter should be equal to or less than the tip diameter.
Testing	Preferably, the dimensions should be determined using non-contact methods, such as a projection microscope. Appropriate gauges or calipers may be used as an alternative. The internal diameter of insertion tube is assessed by using appropriate plug gauges.
1.7 Flexibility test	
Requirement	When tested according to the test method given in section 7.2, the deflection of the horizontal arm from its original position measured at the point on the arm where the load is applied shall be greater than 4.0 mm. A suitable test jig may be used to clamp the T frame and amplify the deflection of the arm, in which case the deflection on the scale shall be greater than that equivalent to a deflection of 4 mm at the point on the arm where the load is applied. This test must be performed on frames prior to assembly. Therefore, verification of conformance with this requirement shall be confirmed at prequalification and requalification.
Testing	According to the test method given in section 7.2.

4. Finished product requirements

These requirements are assessed on finished products during prequalification or surveillance testing. They may also be used for assessing product on a lot-by-lot basis and when doing in-country testing. Testing should be based on the sampling requirements given in section 8. Finished product requirements are set out in Table. 2, classified by category.

Table. 2
Finished product requirements (to be evaluated during prequalification or surveillance testing)

Requirements by category	Specifications
2.1 T frame	
Requirements	All IUDs measured in a test sample shall fall within these ranges: • Length of horizontal arms (total length of both arms): (32 + 1.0/–0.5) mm. • Length of vertical stem: (36 + 1.0/– 0.5) mm. • Diameter of horizontal arm: (1.6 ± 0.1) mm. The measurement should be taken between the collars. • Diameter of vertical stem where it is not covered by copper wire: (1.5 ± 0.1) mm. • The vertical stem shall terminate in a ball. The T piece ball (at the end of vertical stem) shall have a diameter of (3.0 ± 0.7) mm. The junction between the ball and the vertical stem shall preferably be radiused. • The T piece ball (at the end of vertical stem) shall have a hole for securing the thread. A drawing of the T frame is included in Appendix 1.
Testing	Preferably the dimensions should be determined using non-contact methods such as a projection microscope. Appropriate gauges or calipers may be used as an alternative. The diameter of the horizontal arm shall be measured between the collars.
2.2 Thread	
Requirements	The thread shall be knotted to form two tails of approximately equal length. The length of each tail shall be not less than 105 mm and not greater than 125 mm.

Table 2 *continued*

Requirements by category	Specifications
Testing	The length of the tails shall be measured using a calibrated rule from the base of the T piece ball.
2.3 Copper collar	
Requirements	Collar position: (5.4 + 1.3/−0.7) mm from the ends of the T horizontal arm. The measurement shall be taken from the ends of the arms at the edge of the radius. Collar weight shall be (68.7 ± 3.0) milligrams (mg). A drawing of the copper collars is included in Appendix 1.
Testing	Preferably the dimensions should be determined using non-contact methods such as a projection microscope. Appropriate gauges or calipers may be used as an alternative.
2.4 Copper surface area	
Requirements	The nominal surface area shall be 380 mm2 with a tolerance of ± 10% (tolerance specified in ISO 7439). Provided the copper collar and copper wire weights are within the specified limits below, the surface area will comply with the requirements of this specification and ISO 7439 tolerances. Collar weight shall be (68.7 ± 3.0) mg. Wire weight shall be (176 ± 11) mg.
Testing	The weight of the wire and collars shall be determined using a balance after careful removal from the frame.
2.5 Copper wire winding	
Requirements	The wire shall be wound so that it is in contact with the frame and is uniform. The proximal and distal ends of the wire must lie smoothly on the T surface and not protrude beyond the wire profile in order to prevent any chance abrasion of uterine tissue during insertion or in situ. The length of wire protruding from the anchoring hole (the "tag") shall not exceed 10 mm. It shall be bent to point down the vertical stem and not interfere with the position of the arms when the IUD is placed in the insertion device. Both single- and double-wound configurations are acceptable.
Testing	By visual inspection.

Table 2 *continued*

Requirements by category	Specifications
2.6 Insertion tube	
Requirements	The length of the insertion tube shall be (206 ± 2) mm. The internal diameter of the insertion tube shall be (3.7 + 0.2/−0.1) mm. The outside diameter of the insertion tube shall be (4.4 + 0.2/−0.1) mm.
Testing	The internal diameter is assessed by using an appropriate size plug or pin gauge. Measurement will need plug or pin gauges that span the specification measurement: 3.9 mm (tight or not slide in easily), 3.7 mm (go in) and 3.6 mm (tight or slide in easily). The outside diameter should be determined using appropriate ring gauges. The measurements shall be taken at three locations: two within 20 to 30 mm from either end of the tube, and one within ± 10 mm of the midpoint of the tube. Non-contact methods are preferred for the outside diameter.
2.7 Insertion rod	
Requirements	The length of the insertion rod shall be (190 ± 5) mm from handle brace to tip. The insertion rod shall be a snug fit but slide smoothly within the insertion tube and shall not trap the thread. It is recommended that the rod have a thickened section, spline or ridge, to help retain the rod within the insertion tube. The diameter of the insertion rod at tip shall be (2.6 ± 0.2) mm. The rod diameter should be equal to or less than the tip diameter.
Testing	Dimensions shall be determined using appropriate calibrated rules, gauges or calipers or non-contact techniques. Assess the fit of insertion rod by inspection.

Table 2 *continued*

Requirements by category	Specifications
2.8 Insertion tube flange	
Requirements	The shape and dimensions of the central hole shall be such that the specified flange displacement force specification is met.
Testing	By visual inspection.

5. Performance requirements

When tested according to the relevant clause of ISO 7439 or, if appropriate, the specified test method in this document, the performance requirements of the finished product after sterilization shall conform with the requirements specified below. Verification of performance requirements shall be done as part of prequalification or surveillance testing. Testing should be based on the sampling requirements given in section 8. Performance requirements are set out in Table. 3, classified by category.

Table. 3
Performance requirements (to be evaluated during prequalification or surveillance testing)

Requirements by category	Specifications
3.1 Breaking strength	
Requirements	The breaking force of the finished product after sterilization shall be greater than 9.5 N.
Testing	According to the relevant clause of ISO 7439. Further information about testing for breaking force is given in section 7.1.
3.2 Copper collar retention force	
Requirements	The minimum force required to displace a collar on the arm shall be 6.86 N (700 g-force) when tested using a separation speed of (200 ± 20) mm/min.
Testing	According to the test method given in section 7.3.

Table 3 *continued*

Requirements by category	Specifications
3.3 Memory	
Requirements	When the finished product after sterilization is tested according to relevant clause of ISO 7439, the maximum displacement of the horizontal arms from their original position shall be not greater than 5.0 mm.
Testing	According to ISO 7439.
3.4 Thread knot	
Requirements	The knot shall be secure. An insecure thread knot is considered a defect (see part 3.7 of this table, on product defects).
Testing	By visual inspection.
3.5 Insertion rod	
Requirements	The insertion rod shall be a snug fit but slide smoothly within the insertion tube and shall not trap the thread.
Testing	By inspection.
3.6 Flange displacement force	
Requirements	The required force to achieve a steady displacement of the flange shall be between 2.0 and 9.0 N.
Testing	According to the method given in section 7.4.
3.7 Product defects	
Requirements	Finished IUDs should be inspected visually for evidence of visible defects. The severity of defects may vary depending upon the level of impact they have on the safety, effectiveness and acceptability of the product. The number of pieces to be inspected are given in section 8.3. All IUDs comprising the sample shall comply with the requirements for visible defects listed below. Manufacturers and testing laboratories should maintain a list of these defects, with clear definitions and diagrams or photographs to assist both in the assessment of workmanship and in the resolution of any disputes. Below are listed the most common types of defects encountered.

Table 3 *continued*

Requirements by category	Specifications
	Defects Assessed by visual examination, not measurement: • severe tarnishing of the copper collars or wire; • slight tarnishing (acceptable with the agreement of the purchaser); • missing components or empty pouch; • flash on the mould lines of the T frame; • sharp protruding edges or burrs; • unsecured or missing thread (including loose or unsecure knot); • incomplete or deformed ball; • deformed or loose collars; • improperly sealed pouches; • embedded or surface foreign particles on any component within the sealed pouch; • transfer of any printing onto the device; • insertion rod bent or distorted (acceptable at the discretion of the purchaser if still usable); • discoloration of insertion tube or rod.
Testing	By inspection of visible defects.

6. Packaging, labelling and information requirements

Packaging, labelling and information requirements are set out in Table. 4, classified by category.

Table. 4
Packaging, labelling and information requirements

Requirements by category	Specifications
4.1 Device	
Markings requirements	The insertion tube may optionally be printed with depth gauge markings. Manufacturers may mark the frame of the device for identification purposes, provided it does not affect the function and safety of the product.
Testing	By inspection of the product.

Table 4 *continued*

Requirements by category	Specifications
4.2 Individual pouch and insert (primary packaging)	
Packaging requirements	Each TCu380A IUD shall be packed in an individual pouch. All pouches shall be sealed. Packaging materials shall comply with ISO 11607, Part 1. IUDs shall be packed in film–film pouches for better protection and improved confirmation of package integrity, unless sterilization is by ethylene oxide. If an insert is used, it should not affect the safety and performance of the device or be affected by the method of sterilization. The total bioburden of the insert and the device shall be controlled prior to sterilization, in accordance with the validated sterilization protocol.
Testing	Sealed pouch integrity shall be tested according to ASTM D3078 (standard test method for determination of leaks in flexible packaging by bubble emission) using a high vacuum of (24.5 ± 0.5) inches of mercury. This is equivalent to an absolute pressure of (18.4 ± 1.7) kilopascals (kPa) or a gauge reading of (622 ± 12.7) millimetres of mercury (mmHg). If permeable packaging material is used, sealed pouch integrity shall be tested by ASTM F1929 (standard test method for detecting seal leaks in porous medical packaging by dye penetration) using Method B (edge dip method). This method shall only be used for permeable packing materials.
Sealed pouch strength requirements	The peel force shall be not less than 4.4 N and not greater than 19 N for a test sample width of 25.4 mm.
Testing	Testing shall be conducted according to ASTM F88 (standard test method for seal strength of flexible barrier materials). Details regarding the test method are included in section 7.6.

Table 4 *continued*

Requirements by category	Specifications
Labelling requirements	The information shall be printed on the primary container or on an insert that is clearly visible through the primary container. The following information, at a minimum, should be included on the individual pouch or on an insert in the individual pouch. All labelling shall be clearly legible. • Lot identification number. • Month and year of manufacture in a language or languages to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number or abbreviation, as agreed with the buyer. • Insert before date (previously referred to as latest insertion date or expiry date). The insert before date is the date after which the product cannot be inserted in utero. The insert before date shall be printed in a language or languages to be specified by the purchaser and shall be based on the maximum product shelf-life from the date of sterilization. The year will be written as a four-digit number and the month as a two-digit number. If manufacturers choose to include the term "expiry date" on packaging, this must be in brackets below the insert below date and the meaning of expiry date must be defined. • The maximum lifetime in situ. The maximum length of time that the device can remain in utero shall be printed on the primary container. This period shall not exceed 12 years from the date of insertion. • Manufacturer's name and registered address. • The word "Sterile" and the methods of sterilization. • The words "For single use only" or equivalent. • The phrase "Should be administered by a skilled health care provider". • Indication that the device is a TCu380A.
Testing	By inspection of manufacturer's documentation during inspection and visual inspection during prequalification testing and surveillance testing.

Table 4 *continued*

Requirements by category	Specifications
4.3 Consumer packaging	
Definition	A consumer package contains an individual pouch and will commonly contain branding information.
Requirements	The WHO/UNFPA TCu380A IUD technical specification contains no requirements for consumer packaging. If consumer packaging is required, then the full design of the consumer pack should be specified in accordance with the requirements of the programme.
Testing	If consumer packaging is specified, then the consumer packs should be visually inspected for conformance.
4.4 Inner boxes (secondary packaging)	
Definition	Inner boxes, sometimes referred to as secondary packaging or inner cartons, contain specified quantities of IUDs in their individual pouches.
Packaging requirements	The individual pouches shall be packed in inner boxes. The inner boxes shall be constructed of cardboard. A suitable moisture-resistant barrier on inner or outer surfaces of the boxes may be specified by the purchaser. The boxes shall be of sufficient strength and rigidity to retain their shape through every stage of the supply chain.
Labelling requirements	The inner boxes will be marked in a legible manner to describe the contents and to facilitate identification in case of subsequent query. The following information as a minimum shall be included on the inner box. All labelling shall be clearly legible. • Lot identification number. • Month and year of manufacture in a language or languages to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number or abbreviation, as agreed with the purchaser. • Insert before date in a language or languages to be specified by the purchaser. The insert before date shall be based on the maximum product shelf-life from the date of sterilization. The year will be written as a four-digit number and the month as a two-digit number or abbreviation, as agreed with the purchaser.

Table 4 *continued*

Requirements by category	Specifications
	• Manufacturer's name and registered address. • Number of pieces contained in the inner box. • Instructions for shipping and handling, including the phrase "Store in a dry place away from direct sunlight and sources of heat". There is no need to specify a maximum storage temperature on the packaging. • Description of the contents as "medical devices" and indication that the devices are the TCu380A model. • Any specific labelling required by local regulations or regulations in the country to which the product is being shipped. Other information as specified by the purchaser. • Inner box markings can be specified in accordance with programme requirements.
Testing	By visual inspection during prequalification testing or surveillance testing. *Note*: Suitable packaging having the specified labelling might not be available at the time of inspection during prequalification but manufacturers should demonstrate ability to comply with inner pack labelling requirements, for example, through standard operating procedures and past samples.
4.5 Exterior shipping cartons	
Definition	Exterior shipping cartons, sometime referred to as outer boxes or cartons, are the outer containers in which individual pouches within inner boxes are shipped.
Packaging requirements	The inner boxes shall be packed into plastic or other waterproof lining bags, which will be placed in three-wall cartons made from weather-resistant corrugated fibreboard of sufficient strength to avoid products being damaged during shipment. The carton flaps shall be secured with water-resistant adhesive or with appropriate water-resistant tape. Alternatively, the cartons may be secured by plastic strapping at not less than two positions.

Table 4 *continued*

Requirements by category	Specifications
	Alternatively, wire-bound, cleated plywood or nailed wooden boxes are acceptable when lined with a waterproof barrier material. The barrier material must be sealed at the edges with waterproof tape or adhesive, and there must be no sharp protrusions inside the boxes.
Labelling requirements	The exterior shipping cartons will be marked in a legible manner to describe the contents and to facilitate identification in case of subsequent query. The following information as a minimum shall be included on the exterior shipping carton. All labelling shall be clearly legible. • Lot identification number. • Manufacturer's name and registered address. • Month and year of manufacture in a language or languages to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number or abbreviation, as agreed with the buyer. • Number of pieces contained in the shipping carton. • Insert before date in a language or languages to be specified by the purchaser. The year will be written as a four-digit number and the month as a two-digit number. • Instructions for shipping and handling, including the phrase "Store in a dry place away from direct sunlight and sources of heat". There is no need to specify a maximum storage temperature on the packaging. • Description of the contents as "medical devices". • Any specific labelling required by local regulations or regulations in the country to which the product is being shipped. • Other information as specified by the purchaser.
Testing	By inspection of manufacturer's documentation during inspection and visual inspection during prequalification testing and surveillance testing.

Table 4 *continued*

Requirements by category	Specifications
4.6 Packaging and labelling: visible defects	
Individual pouch and insert	Individual pouches should be inspected visually for evidence of visible defects. Common individual pouch and insert defects include: • discoloured film and labels; • missing or incorrect labelling information, as specified in category 4.2 above; • pouch with open or damaged seals; • unclear and not readily legible printing on individual pouch and insert.
Consumer packaging	Not specified
Inner boxes	Inner boxes should be inspected visually for evidence of visible defects. Common inner box defects include: • damaged boxes that may affect the integrity, quality or distribution of the IUDs inside; • empty or partially filled inner boxes; • missing or incorrect labelling information, as specified in category 4.4 above; • unclear and not readily legible printing on inner box.
Exterior shipping cartons	Exterior shipping cartons should be inspected visually for evidence of visible defects. Common exterior shipping carton defects include: • damaged shipping cartons that may affect the integrity, quality or distribution of the IUDs inside; • empty or partially filled exterior shipping cartons; • missing or incorrect labelling information, as specified in category 4.5 above; • unclear and not readily legible printing on exterior shipping cartons.
Testing	By inspection of visible defects.

7. Laboratory test methods

Further details of the test procedures are given in this section. These include modification to the test methods given in ISO 7439 or test methods that are specific to the TCu380A IUD.

All testing shall be performed at a temperature of (23 ± 2) °C.

7.1 Breaking strength

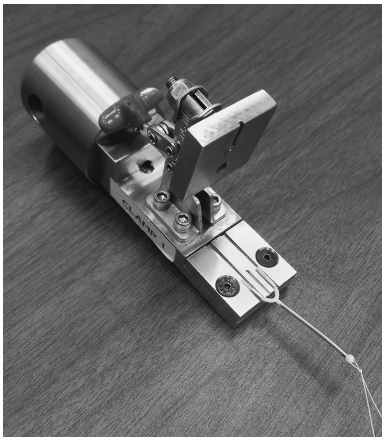
The IUD shall be tested according to ISO 7439 with the arms of the T frame bent upward and clamped parallel to each other at a distance of (8 ± 2) mm apart, with a single tail thread clamped at a distance of 5 mm from the point of attachment to the IUD. The arms of the T frame shall be clamped by the copper collars only.

Conditioning, as specified in the relevant clause of ISO 7439, needs to be carried out only in the case of dispute.

An example of a suitable clamp for holding the device is shown in Fig.2(a), and Fig.2(b) shows the test in progress.

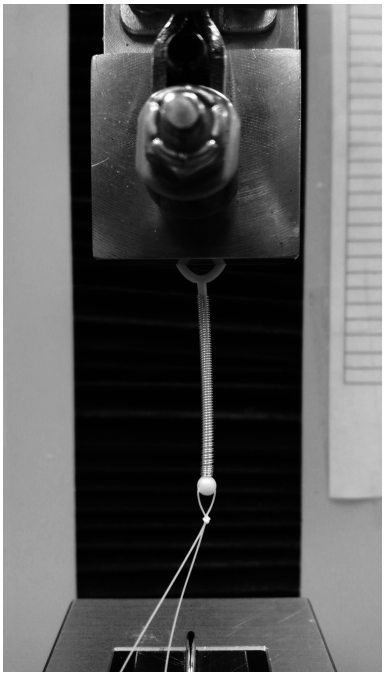
Fig. 2
Testing breaking strength

(a) Breaking force test clamp



Source: FHI 360.

(b) Breaking strength test



Source: FHI 360.

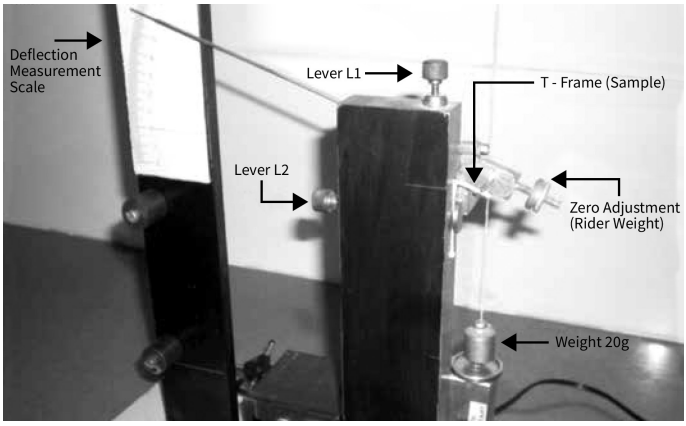
7.2 Flexibility test

This test is used by the manufacturer to confirm the flexibility of the frame. A 20 gram (g) weight is applied to one of the horizontal arms of the T frame for a period of 30 seconds at a distance of 12 mm from the vertical arm. The deflection of the arm from the horizontal position is measured at the point on the arm where the load is applied.

A suitable test jig may be used to clamp the T frame and measure the amplitude of the deflection. A pivoted needle or lever may be used to amplify the deflection of the horizontal arm. A photograph of a suitable test jig is shown in Fig. 3. Technical drawings for this measurement equipment can be requested from UNFPA. If such a test jig is used, the T frame arm deflection may be converted into a scale reading using the appropriate amplification factor for the jig.

The test shall be carried out at a temperature of (23 ± 2) °C on frames that are at least 96 hours old from the time of moulding. Before testing, the T frames shall be stored for at least 6 hours at the test temperature.

Fig. 3
Flexibility apparatus



Source: Corporate Channels India Pvt. Ltd.

7.3 Copper collar retention force

Testing shall be conducted using a suitable measuring device, such as a tensile testing machine, that can measure the displacement force at a separation speed of (200 ± 20) mm/min.

During the copper collar retention force test, the device shall be clamped by the collar on one of the arms, using a suitable jig if necessary, and the opposing arm shall be gripped in the opposite clamp. The force applied to the clamped collar shall not be sufficient to crush the collar and cause it to tighten onto

the arm. This can be achieved, for example, by gripping the collar with a clamp having a groove milled with a 1.59 mm (1/16 inch) ball end mill to a depth of 1.38 mm, or about 65% of the collar diameter, to prevent crushing the collar.

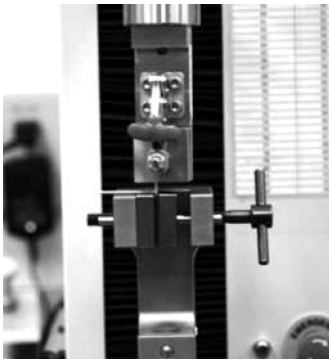
Alternatively, one collar may be clamped in one jaw with sufficient force to ensure that it is partially crushed and tightened onto the arm so that there is no slippage during the test. The other collar shall be clamped lightly in the opposing jaw so that it is not crushed and tightened onto the arm. This can be achieved, for example, by using a clamp having a groove milled with a 1.59 mm (1/16 inch) ball end mill to a depth of 1.38 mm, or about 65% of the collar diameter, to prevent crushing the collar.

Pictures of suitable apparatus for the copper collar retention force test are presented in Fig. 4(a–c).

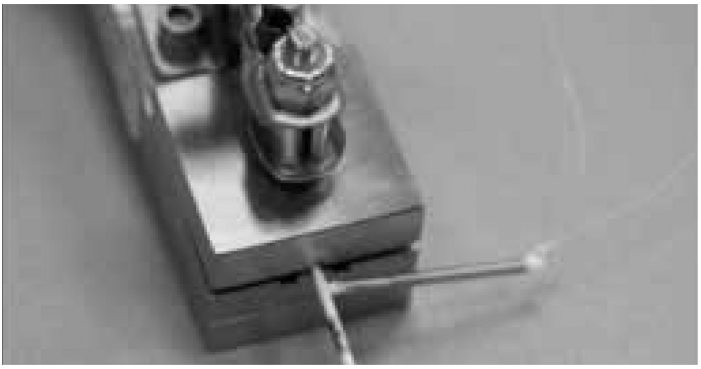
Fig. 4
Apparatus for copper collar retention force test

(a) Copper collar retention force: clamp

(b) Copper collar retention force: test set-up



(c) Copper collar retention force: IUD in clamp



Source: FHI 360.

7.4 Flange displacement force

Testing shall be conducted using suitable measuring equipment, such as a tensile testing machine, that can measure the displacement force at a displacement speed of (200 ± 20) mm/min. A suitable test rig will be required to clamp the tube and apply a displacement force to the flange. An appropriate load cell should be used, such as a 50 N or 10 N load cell.

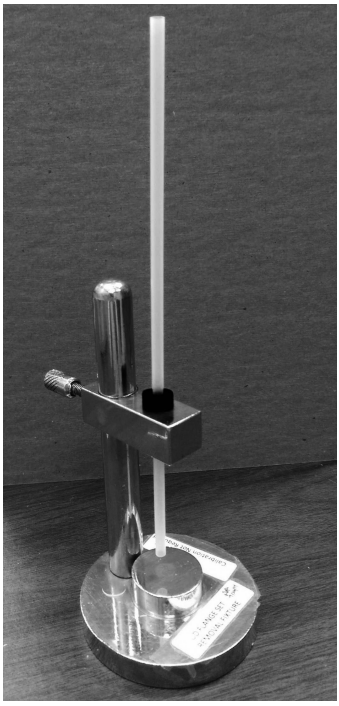
The displacement force should be assessed after any initial "set" is overcome. Record the highest force measured once the flange is moving.

To remove set, the flange should be moved over a distance of 1 centimetre (cm) along the tube in the same direction as it will be moved during the test. This can be done manually or by using a suitable jig. The displacement force shall be measured immediately after removal of the set.

An example of a suitable jig for removing the set is shown in Fig. 5(a), and the flange force test set-up is shown in Fig. 5(b).

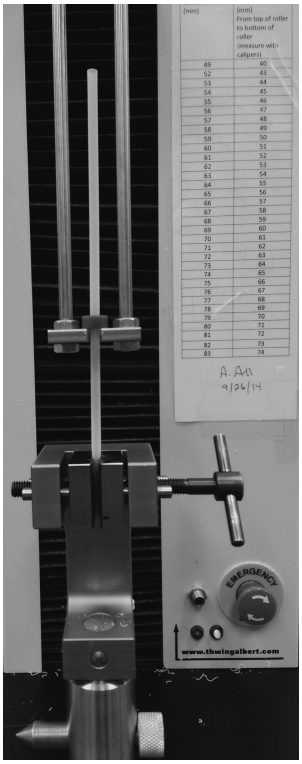
Fig. 5
Testing flange displacement force

(a) Flange force set removal jig



Source: FHI 360.

(b) Flange force test set-up

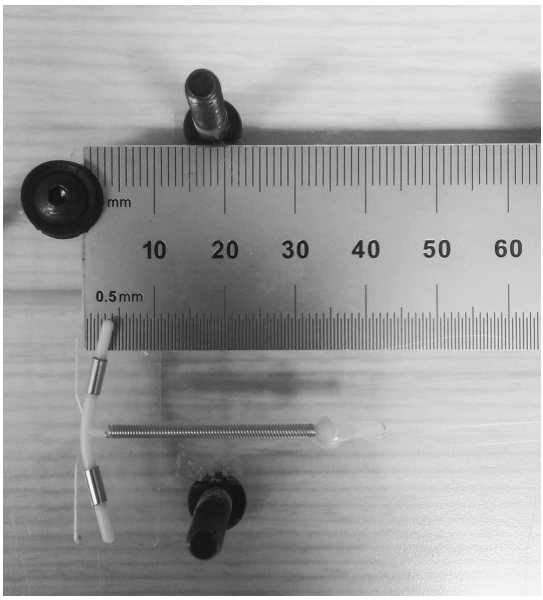


Source: FHI 360.

7.5 Memory test

The finished product after sterilization shall be tested according to the relevant clause of ISO 7439 for recovery after deformation (viscoelastic property). The maximum displacement of the arms from their original position shall be not greater than 5.0 mm. Fig. 6 shows an example of how the displacement is measured.

Fig. 6
Memory test



Source: FHI 360.

7.6 Sealed pouch peel strength requirements

Carefully open at the end of the individual pouch as directed on the insert. This end normally has an angled shaped seal. Limit the extent of opening so it is just sufficient to be able to withdraw the pouch contents. Carefully remove the contents of the pouch.

Cut two strip samples using a 25.4 mm wide die. If a 25.4 mm wide die is not available, a die within the range of 20–40 mm may be used and the minimum and maximum peel strength requirements, as specified in category 4.2 of Table. 4, shall be adjusted on a pro rata basis. The first sample shall be cut across at the approximate midpoint of the individual pouch. The second sample shall be cut parallel to the long axis of the individual package incorporating the intact end seal at the opposite end to where the pouch has been opened.

For the sample cut across the individual pouch, one of the sealed ends shall be cut off leaving a V-shaped sample, as indicated in Fig. 7.

Fig. 7
Sealed pouch peel strength: test set-up

Source: FHI 360.

The seal strength of the end seal and side seal samples shall then be determined according to the following methods:

- If the packaging is made from two equally flexible materials, Technique B of ASTM F88 shall be used (sample supported at an angle of 90° by hand).
- If a rigid material is used as part of the pack, for example, a moulded tray, then Technique C of ASTM F88 shall be used (sample supported at an angle of 180°).

7.7 Biocompatibility evaluation

Biocompatibility evaluation shall be conducted according to the methods described in the relevant part of ISO 10993. When testing is necessary, it is recommended that extracts are used to assess biocompatibility. Suitable extraction media may include culture medium with or without serum, serum and saline, depending upon the specific test that is being conducted. Extraction shall be conducted according to ISO 10993 12. The recommended extraction conditions are (72 ± 2) hours at (50 ± 2) °C. The recommended ratio of sample to extraction medium is 0.2 g per 1 mm. It is permissible to test either the compounded polymers or the moulded frame and thread. If the finished products are used for this testing, the copper wire and collars should be removed to prevent the risk of false positive results.

Some regulatory authorities may require additional testing or certain tests to also be done using non-polar extraction media, such as pharmacopoeial

grades of cottonseed or sesame oil. Specific test requirements should be confirmed locally before undertaking any testing.

For cytotoxicity testing, it is recommended that quantitative tests are used. A suitable test can be selected from the following annexes of ISO 10993-5:

- Annex A: Neutral red uptake (NRU) cytotoxicity test
- Annex B: Colony formation cytotoxicity test
- Annex C: MTT cytotoxicity test
- Annex D: XTT cytotoxicity test.

Results should be reported as IC50 or Viab % values, as appropriate.

Laboratories with accreditation for these tests shall be used for all biocompatibility testing. The results shall be interpreted by a suitably qualified toxicologist or other suitable expert.

8. Sample sizes and acceptance criteria for testing

Significant changes have been made to the sample sizes and acceptance criteria compared with the 2010 specification. Given the characteristics of the products, the nature of the manufacturing processes and, for the most part, the relatively small lot sizes used by many manufacturers, fixed sample sizes and specific acceptance criteria have been adopted rather than specified inspection levels and AQLs. Sample sizes vary depending upon the purpose of testing being carried out.

8.1 Sample sizes and acceptance criteria for WHO/UNFPA prequalification testing

Sample sizes and acceptance criteria for prequalification testing are given in Table. 5. These sample sizes are intended to provide a very high level of confidence that the product conforms to the specification requirements. They also take account of difficulties often encountered by inspectors and sampling agencies when trying to take samples for prequalification testing.

8.2 Samples sizes and acceptance criteria for continuing series of lots

Sample sizes and acceptance criteria for continuing series of lots are given in Table. 6. These sample sizes are applicable when a series of at least five lots is being assessed. They can be used, for example, by purchasers who wish to conduct preshipment or confirmatory testing.

They are also recommended when in-country testing is carried out, and can also be used by manufacturers for assessing the conformance of production lots.

For any requirement, there shall be no nonconforming units in the sample tested. If at any time two out of five (or fewer than five) consecutive lots are found to be nonconforming on any specific requirement, then the number of samples used to assess the conformity for future lots shall be increased to the number given in brackets for that specific requirement (tightened inspection). The sample sizes given in the brackets shall continue to be used until five consecutive lots have been found to be acceptable for that requirement (that is, change from tightened inspection to normal inspection). The sample sizes for continuing series of lots specified in Table. 6 apply only when five or more lots are being assessed.

In addition to using the sample sizes and acceptance criteria given in Table. 6 for assessing production lots, it is recommended that manufacturers adopt statistical process control procedures, such as the use of control charts, to ensure that their products conform to the specification. It is also strongly recommended that manufacturers conduct periodic process capability studies to confirm that their processes are operating within acceptable tolerances.

8.3 Sample sizes and acceptance criteria for isolated lots

Sample sizes and acceptance criteria for assessing the conformity of fewer than five lots are given in Table. 6. These sample sizes are recommended for surveillance testing where only a limited number of lots are assessed. They can also be used for confirmatory or in-country testing on small shipments and for testing retained or returned samples from lots following complaints or in-use failures. The sample sizes have been increased to provide a higher level of confidence in deciding whether or not an individual lot conforms to the specification requirements.

A total sample of 600 IUD pieces taken from between 1 and 20 lots, depending upon the production plan of the manufacturer, is required for testing. This includes a small contingency (20) in case there are problems with any of the samples or tests. Please note the total sample size for prequalification is 600 pieces, irrespective of the number of lots the sample is taken from.

UNFPA will determine the sampling plan following review of production plans supplied by the manufacturer.

The IUDs contained in the packages subjected to the package seal integrity and peel strength tests can be used for testing. All dimensional measurements can be conducted on the same IUD samples.

Table. 5
Samples sizes and acceptance criteria for WHO/UNFPA prequalification testing of the TCu380A IUD

Requirement	Prequalification		Category (see Tables. 1–4)
	Sample size from all lots	Maximum permitted nonconforming units per sample	
Frame dimensions			
Length of horizontal arms	50	2	2.1
Length of vertical stem			
Diameter of horizontal arm			
Diameter of vertical stem			
T piece ball diameter			
Thread length	50	2	2.2
Copper collars			
Position	50	2	2.3
Weight			
Copper collar retention force			3.2
Copper wire			
Copper wire weight	125	2	2.4
Copper wire winding	50	2	2.5
Insertion tube			
Insertion tube dimensions	50	2	2.6
Length			
Internal diameter			
External diameter			
Insertion rod dimensions			
Length	50	2	2.7
Diameter at tip			
Fit in insertion tube			3.5

Table 5 *continued*

Requirement	Prequalification		Category (see Tables. 1–4)
	Sample size from all lots	Maximum permitted nonconforming units per sample	
Finished IUD after sterilization			
Breaking strength	200	5	3.1
Memory	80	3	3.3
Flange displacement force	50	2	3.6
Packaging			
Sealed pouch integrity	500	0	4.2
Package pouch peel strength			
End seal	80	2	5.2
Side seal	80	2	
Product defects			
Defects (including knot security)	125	3	3.7
Packaging defects (inner boxes and exterior shipping cartons, to be evaluated by inspection company)			
Individual pouch	These will be evaluated by the inspectors or by a sampling or inspection agency Assessment will be based on ability to comply with requirements		4.6
Inner box (if consignment includes less than 13 inner boxes, inspect all boxes)			4.6
Exterior shipping carton (if consignment includes less than 13 exterior shipping cartons, inspect all boxes)			4.6

Table. 6

Sample sizes and acceptance criteria for testing of continuing series of lots and isolated lots of the TCu380A IUD

Requirement	Continuing series of lots		Isolated lots (surveillance testing)		Category (see Tables. 1–4)
	Sample size for normal (tightened) inspection	Maximum permitted nonconforming units per sample	Sample size (pieces)	Maximum permitted nonconforming units per sample	
Frame dimensions					
Length horizontal arms	8 (13)	0	32	1	2.1
Length vertical stem					
Diameter horizontal arm					
Diameter vertical stem					
T piece ball diameter					
Thread length	8 (13)	0	32	1	2.2
Copper collars					
Position	8 (13)	0	32	1	2.3
Weight					
Copper collar retention force					3.2
Copper wire					
Copper wire weight	20 (32)	0	80	1	2.4
Copper wire winding	8 (13)	0	32	1	2.5

Table 6 *continued*

Requirement	Continuing series of lots		Isolated lots (surveillance testing)		Category (see Tables. 1–4)
	Sample size for normal (tightened) inspection	Maximum permitted nonconforming units per sample	Sample size (pieces)	Maximum permitted nonconforming units per sample	
Insertion tube					
Insertion tube dimensions	8 (13)	0	32	1	2.6
Length					
Internal diameter					
External diameter					
Insertion rod dimensions					
Length	8 (13)	0	32	1	2.7
Diameter at tip					
Fit in insertion					3.5
Tube					
Finished IUD after sterilization					
Breaking strength	13 (20)	0	50	1	3.1
Memory	8 (13)	0	32	1	3.3
Flange displacement force	8 (13)	0	32	1	3.6

Table 6 *continued*

Requirement	Continuing series of lots		Isolated lots (surveillance testing)		Category (see Tables. 1–4)
	Sample size for normal (tightened) inspection	Maximum permitted nonconforming units per sample	Sample size (pieces)	Maximum permitted nonconforming units per sample	
Packaging					
Sealed pouch integrity	125 (200)	0	125	0	4.2
Sealed pouch peel strength					
End seal	13 (20)	0	50	1	4.2
Side seal					
Product defects					
Defects (including knot security)	13 (20)	0	50	1[a]	3.7
Individual pouch	13 (20)	0	13	0	4.6
Inner box (if consignment includes less than 13 inner boxes, inspect all boxes)					
Exterior shipping carton (if consignment includes less than 13 exterior shipping cartons, inspect all boxes)					

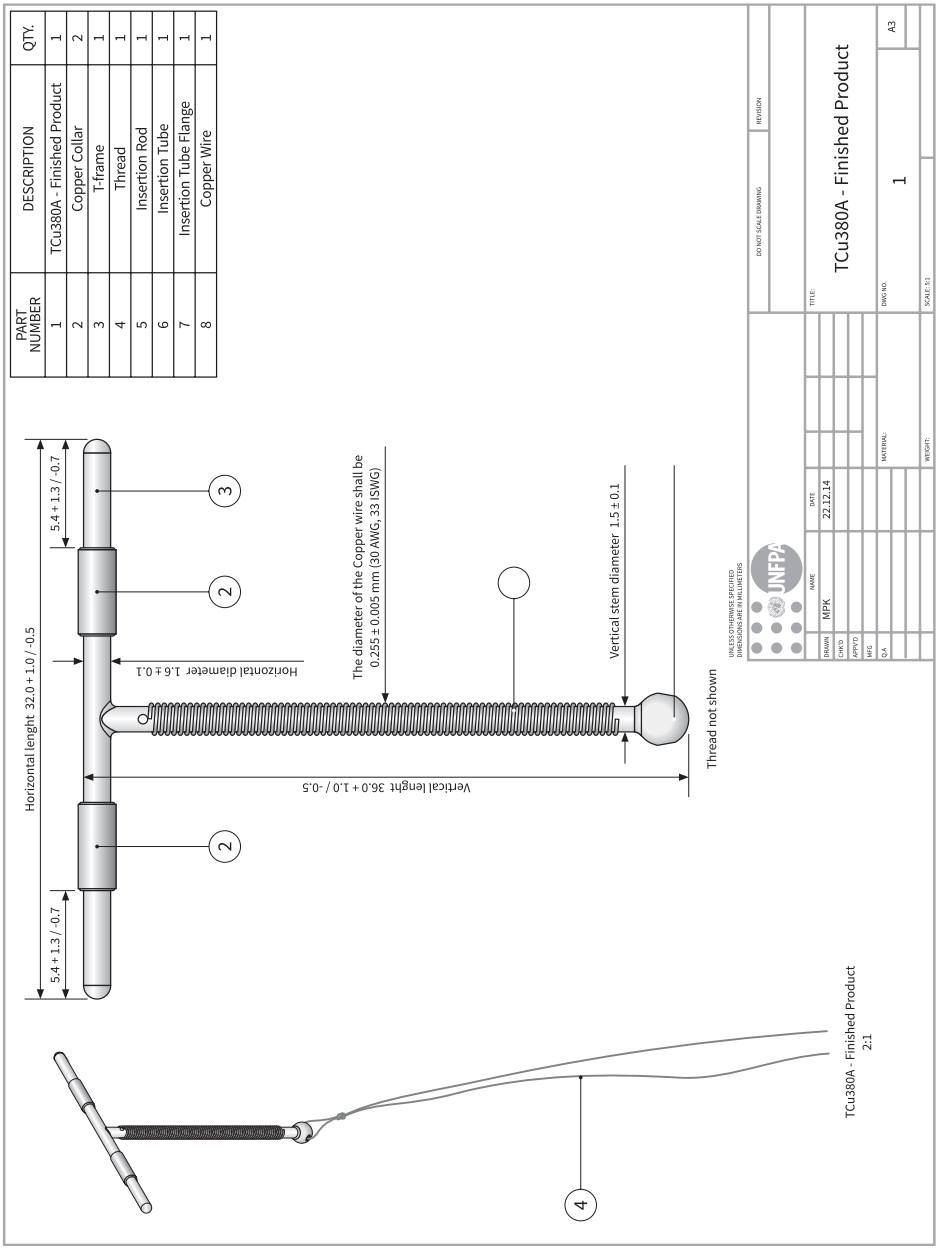
[a] When testing lots that have been stored for over a year, the maximum permitted number of nonconforming units shall be raised to three for slight tarnishing and bent or distorted insertion rods.

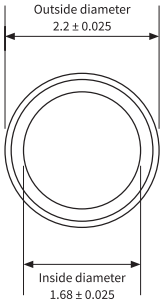
References

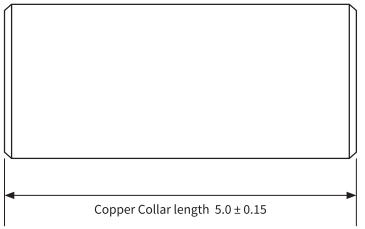
1. ISO 7439:2015. Copper-bearing contraceptive intrauterine devices – Requirements and tests. Geneva: International Organization for Standardization; 2015.
2. ParaGard Copper T model TCU 380A intrauterine contraceptive. Population Council New Drug Application (NDA) 18-680, 1984.
3. TCu380A intrauterine contraceptive device: WHO/UNFPA technical specification and prequalification guidance 2016. Geneva: World Health Organization and United Nations Population Fund; 2016.
4. Guidelines relating to the application of: The Council Directive 90/385/EEC on active implantable medical devices and The Council Directive 93/42/EEC on medical devices (MEDDEV 2. 1/3 rev3, clause B.4.1). European Commission DG Enterprise and Industry; 2009.
5. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. European Parliament and Council of the European Union; 2017.

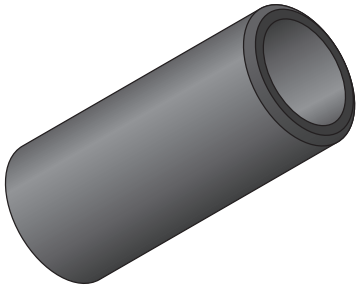
Appendix 1

IUD technical drawings









UNLESS OTHERWISE SPECIFIED
DIMENSIONS ARE IN MILLIMETERS

UNFPA

	NAME	DATE
DRAWN	MPK	23.12.14
CHK'D		
APPV'D		
MFG		
Q.A		

MATERIAL:

WEIGHT:

DO NOT SCALE DRAWING | REVISION

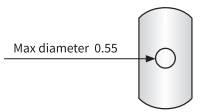
TITLE:

Copper Collar

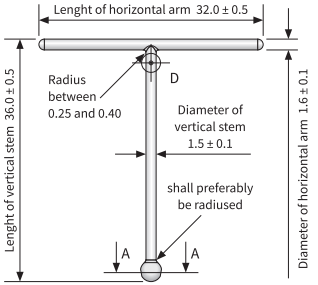
DWG NO. 2

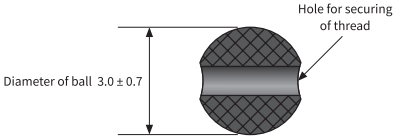
A3

SCALE:



DETAIL D
SCALE 10:1





SECTION A-A
SCALE 10:1

UNLESS OTHERWISE SPECIFIED
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UNFPA						DO NOT SCALE DRAWING	REVISION
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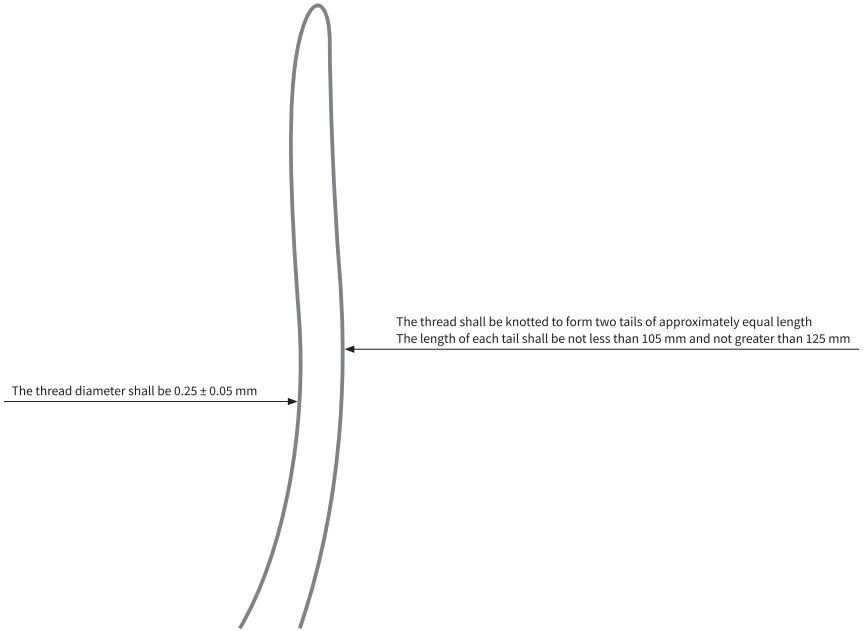
CHK'D							
APPV'D							
MFG							
Q.A				MATERIAL:		DWG NO. 3	A3
						SCALE:	



UNLESS OTHERWISE SPECIFIED
DIMENSIONS ARE IN MILLIMETERS

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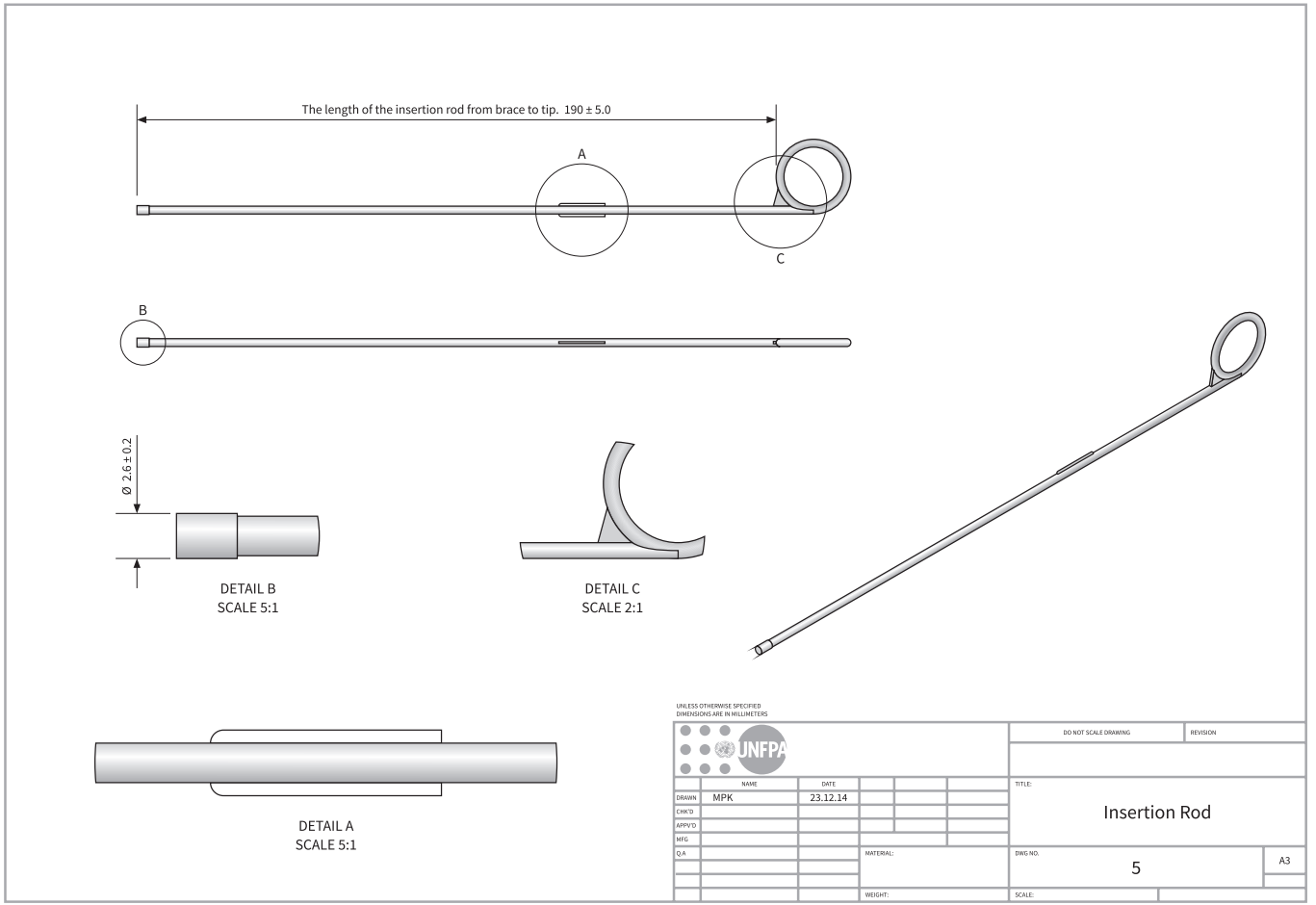
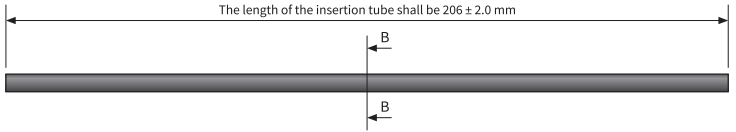
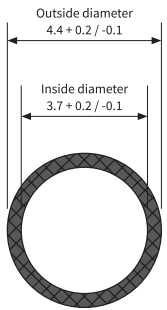
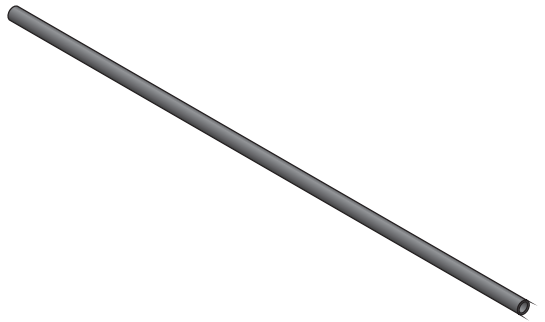
CHK'D							
APPV'D							
MFG							
Q.A				MATERIAL:		DWG NO.	A3
						4	
				WEIGHT:		SCALE:	


The length of the insertion rod from brace to tip. 190 ± 5.0
A
C
B
Ø 2.9 ± 0.2
DETAIL B
SCALE 5:1
DETAIL C
SCALE 2:1
DETAIL A
SCALE 5:1
UNLESS OTHERWISE SPECIFIED
DIMENSIONS ARE IN MILLIMETERS
UNFPA
DO NOT SCALE DRAWING
REVISION
NAME
DATE
DRAWN
MPK
23.12.14
CHK'D
APPV'D
MFG
Q.A
MATERIAL:
WEIGHT:
TITLE:
Insertion Rod
DWG NO.
5
A3
SCALE:





SECTION B-B
SCALE 10:1



UNLESS OTHERWISE SPECIFIED
DIMENSIONS ARE IN MILLIMETERS

UNFPA

	NAME	DATE
DRAWN	MPK	23.12.14
CHK'D		
APPV'D		
MFG		
Q.A		

DO NOT SCALE DRAWING | REVISION

TITLE: Insertion Tube

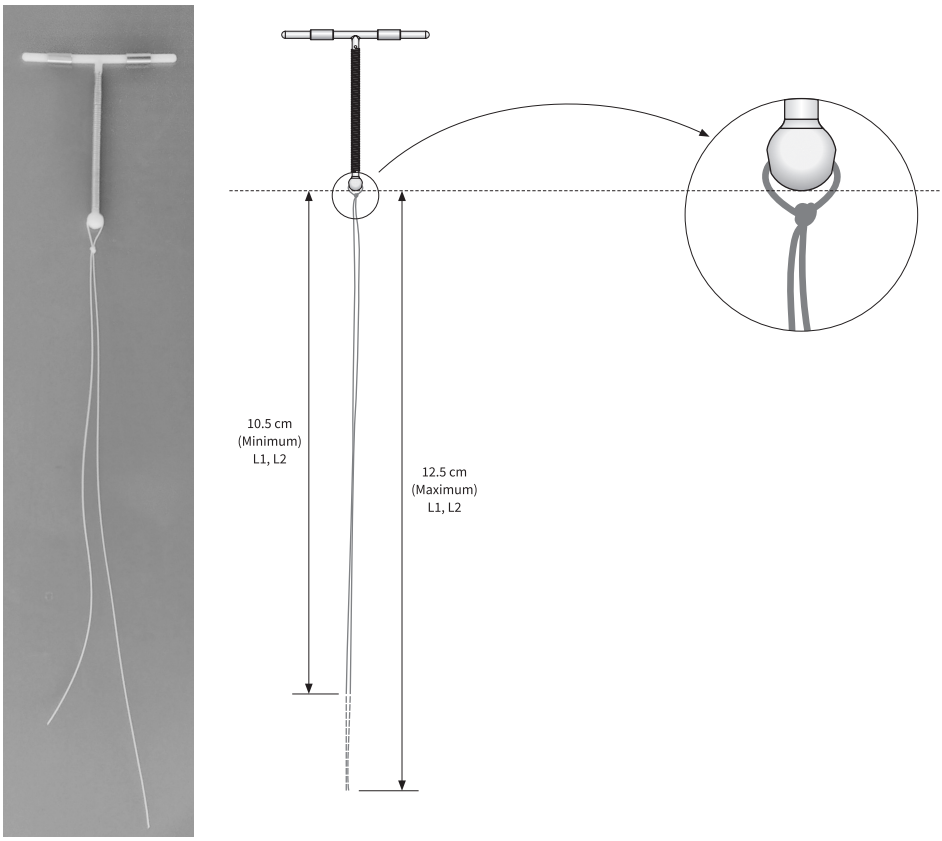
MATERIAL:

DWG NO. 6

A3

WEIGHT:

SCALE:



Permitted Length of each strand (i.e. L1, L2) = 105 mm — 125 mm
Note: The thread shall be knotted to form two tails of approximately equal length as shown in photograph / diagram above. After knotting the length of each straightened tail, shown as over-lapping each other in the diagram, shall be not less than 105 mm and not greater than 125 mm

Appendix 2

Guidance for bioburden control and terminal sterilization

1. Introduction and WHO/UNFPA requirement

The sterility assurance level (SAL) required in this technical specification and for the World Health Organization (WHO)/United Nations Population Fund (UNFPA) prequalification for terminally sterilized intrauterine devices (IUDs) is 1×10^{-6}. Sterility testing alone following terminal sterilization cannot provide adequate confirmation of sterility at this assurance level even when a large sample size is tested. The risk of the testing leading to false positives further rules this out as a single viable approach to verification of the achieved SAL.

Sterility assurance at this level can be achieved by real-time release testing (parametric release), which is in turn achieved by a combination of the following:

- validation and routine control of the sterilization process;
- validation, control and monitoring of the bioburden on the product.

This is the approach adopted by the sterilization standards that are required and outlined in this WHO/UNFPA TCu380A IUD technical specification and prequalification guidance document. All prequalified IUD manufacturers are required to demonstrate conformance with the International Organization for Standardization (ISO) 11737-1 requirements for establishment of acceptable limits for bioburden on a medical device based on historical data. The following text provides guidance on achieving the recommended SAL and demonstrating conformance with ISO 11737-1.

2. Sterility assurance level

The SAL is the probability of a single unit being non-sterile after it has been subjected to sterilization. The SAL shall be at least 1×10^{-6}.

3. Normative standards for sterility assurance

The following standards and guidance are recommended. The manufacturer should ensure conformance with the latest published version of the applicable standards that apply to their sterilization process and bioburden assessment test methods. The latest edition of the standards shall be used by manufacturers.

ISO 13485: Medical devices – Quality management systems – Requirements for regulatory purposes.

ISO 17665: Sterilization of health care products – General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process.

ISO 11135: Medical devices – Validation and routine control of ethylene oxide sterilization.

ISO 11137-1: Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.

ISO 11137-2: Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose.

ISO 11137-3: Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects.

ISO TS 13004: Sterilization of health care products – Radiation – Substantiation of selected sterilization dose: Method VDmaxSD.

ISO 14937: Sterilization of health care products – General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process.

ISO 11737-1: Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products.

ISO 11737-2: Sterilization of medical devices – Microbiological methods – Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process.

European Medicines Agency Committee for Medicinal Products for Human Use – Guideline on Real-Time Release Testing (formerly Guideline on Parametric Release). EMA/CHMP/ QWP/811210/2009-Rev1 (2012).

4. Sterilizer process validation

Prequalified manufacturers of IUDs are required to use terminal sterilization facilities that are certified to ISO 13485 and are in conformance with the applicable sterilization standards appropriate for the sterilization of IUDs, such as ISO 11137 for radiation sterilization or ISO 11135 for ethylene oxide sterilization. Radiation is often considered the preferred sterilization method for IUDs, despite the potential adverse effects radiation may have on some materials. Radiation permits the use of impermeable packaging pouches made of

a film–film layer combination that can reduce the risk of compromising sterility compared to the use of gas permeable pouches made of film–gas permeable synthetic layer combinations that are required for ethylene oxide (or other gas) terminal sterilization methods.

The principles of sterilizer process validation and control are similar for radiation, ethylene oxide and other sterilization methods, but this guidance focuses on radiation sterilization for the above-mentioned reasons. In most cases, radiation sterilization is subcontracted to a service provider and, in such cases, it is important to note that the IUD manufacturer is responsible for a high degree of control over the service provider.

Terminal radiation sterilization standards provide at least two methods of establishing the applicable radiation dose. In the first method, the sterilization dose is set based on knowledge of the number of microorganisms comprising the bioburden on the product and their resistance to radiation. In the second method, the dose is fixed at a defined level (such as 25 kilogray (kGy) or 15 kGy) and the primary manufacturer has to substantiate that the selected sterilization dose is capable of achieving the specified requirements for sterility.

Of the two methods, using a fixed dose (such as 25 kGy) is widely used for medical devices and is preferred for the terminal sterilization of TCu380A IUDs. This dose is widely used within the industry and has been established over many years of use as being safe and effective. If the dose is changed, then validation by the methods specified in the appropriate standards would be required to confirm that the sterility, safety and effectiveness of the IUDs are not compromised. A prequalified TCu380A IUD manufacturer would also have to obtain the prior agreement from UNFPA for the change by submitting a validation protocol and a report supporting the change for review by an appropriate technical expert.

Validation of the sterilization process is specified in the applicable sterilization standards (such as for radiation in ISO 11137-1 and for ethylene oxide in ISO 11135-1).[2] Periodic process validation of the sterilizer by the operator or supplier and reports of these validations are required. The prequalified IUD manufacturer is expected to monitor this to obtain and maintain copies of the validation reports and to review them as part of supplier evaluation and control. The IUD manufacturer should include these validation reports in any audits of the sterilization supplier that they carry out. Typically, the frequency of such full audits is between one and two years, not more.

[2] See section 9 of both ISO 11137-1: Sterilization of health care products – Radiation, and IS0 11135: Medical devices – Validation and routine control of ethylene oxide sterilization.

5. Sterilizer process control

The standards provide details on the routine monitoring and control of sterilization processes. For radiation sterilizers, this includes the use of chemical dosimeters.[3] Biological indicators, such as bacterial spore strips, and chemical indicators are used for process control of ethylene oxide and other gas sterilizers.[4] All aspects of the effective use of these dosimeters or indicators should be appropriately monitored by the IUD manufacturer for product release and as part of their routine auditing of the supplier. Confirmation of the acceptable levels of sterilizer monitoring should be included in any audits of the sterilization supplier by the IUD manufacturer.

The IUD manufacturer should review and monitor the other routine controls of the sterilizer specified in the standards. For example, ISO 11137-1 requirements can include the following.

- Sterilization dose audits can be conducted to monitor the continued effectiveness of the established sterilization dose and the resistance of the product bioburden to radiation (Clause 12.1.1).
- The frequency of sterilization dose audits shall be based on review and records of the manufacturing process, the control and monitoring procedures for the manufacturing process and, particularly, manufacturing steps that may affect the product bioburden or its resistance (Clause 12.1.3).
- The time interval between dose audits can only be increased if four consecutive dose audits show no change or if the bioburden has remained stable in number and type (Clause 12.1.3.2).
- The maximum dose audit interval is typically one year (Clause 12.1.3.3).
- A dose audit must be completed for every batch if the batch manufacturing interval is greater than the specified dose audit interval (Clause 12.1.3.4).

Manufacturers should note the requirement that "radiation sensitive visual indicators shall not be used as proof of adequate radiation processing or as the sole means of differentiating irradiated products from non-irradiated products"[5] in respect of terminal radiation sterilization.

[3] See section 10 of both ISO 11137-1: Sterilization of health care products – Radiation, and IS0 11135: Medical devices – Validation and routine control of ethylene oxide sterilization.

[4] IS0 11135: Medical devices – Validation and routine control of ethylene oxide sterilization.

[5] See ISO 11137-1: Sterilization of health care products – Radiation – Clause 10.4.

Maintaining process effectiveness is specified differently for each terminal sterilization method.[6] In general, the sterilization standards specify that knowledge of the bioburden on the product is required for conformance according to the standard. The IUD manufacturer shall make it clear to the operator of the sterilization facility that terminal sterilization is a process of joint responsibility. For terminal sterilization by radiation operating according to the standard, monitoring of bioburden is required at a maximum interval of three months (or less over time based on historical data),[7] but it is recommended by UNFPA that every lot should be tested for bioburden.

6. Product bioburden validation

Manufacturers must maintain product bioburden levels below the validated limit for the sterilization process. This is achieved by a combination of process validation and control.

6.1 Scope of process bioburden validation

Bioburden validation of the product shall encompass all of the processes that can directly affect product bioburden. This will include the manufacturing process and manufacturing steps that affect bioburden or its resistance; control and monitoring procedures for the manufacturing process; the manufacturing environment, particularly the extent of microbiological control and monitoring and available data on the stability of the manufacturing environment over time; and the controls on the health, cleanliness and clothing of personnel in the manufacturing area and all other good manufacturing practice (GMP)-related procedures. Therefore, product bioburden cannot be validated in isolation from the process validation and control of those processes that directly affect it.

6.2 Development of "alert "("warning") and "action" levels for product bioburden

Acceptable limits for bioburden shall be specified on the basis of previously generated data and shall be documented. If these limits are exceeded, corrective action shall be undertaken. It is therefore recommended that process control of bioburden should be based on setting "alert" (or "warning") and "action" levels.[8]

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[6] See section 12 of ISO 11137-1: Sterilization of health care products – Radiation, IS0 11135: Medical devices – Validation and routine control of ethylene oxide sterilization, and ISO 14937: Validation and routine control of any alternative sterilization process.

[7] See 12.1.2.1 of ISO 11137-1: Sterilization of health care products – Radiation.

[8] Winters M, Patch E, Wangsgard W, Ferry A, Bushar H. Establishing bioburden alert and action levels. Nelson Laboratories; 2017.

This is considered best practice in the medical device industry. As part of bioburden validation, therefore, manufacturers should establish these limits from historical bioburden data.

In order to establish these levels, it is necessary to characterize the distribution of the bioburden and its variability and obtain appropriate statistically based limits from the data.

The distribution of the product bioburden is established from historical data and more frequent sampling than the recommended quarterly maximum for routine monitoring.[9] Product bioburden samples should be representative of the manufacturing environment and should include, as far as reasonably practicable, samples from just before any routine fumigation or other key environmental maintenance operations, and the loading of the environment with personnel should reflect normal production levels. Using standard deviations of the data is considered to be a safe assumption that does not necessitate prior consideration of the normality of the data.[10]

In common with normal quality assurance procedures, the alert level can be set at two times the standard deviation and the action level at three times the standard deviation, and a limit at 10 times the expected or mean level after the correction factor has been applied (see below). The alert level can be set at two standard deviations from the expected mean level, since 95.44% of all measurements should fall in this range, and the action level set at three standard deviations, since 99.73% of all measurements should fall in this wider range, assuming that there has been no shift in the mean.

For established radiation doses, the measured bioburden levels should be compared with the product bioburden limit values specified in the standard.[11]

6.3 Correction factor for recovery of microorganisms

ISO 11137-1 (the bioburden standard) requires that during method validation a correction factor is determined based on the recovery efficiency of the removal of active microorganisms from the product in the process of determining product bioburden.[12]

This correction factor is required before the statistics from product bioburden can be safely translated into out-of-specification limits, to include alert (warning) and action limits.

[9] See 12.1.2.1 of ISO 11137-1: Sterilization of health care products – Radiation.

[10] Winters et al. 2017.

[11] See ISO 11137-2: Sterilization of health care products – Radiation, Table 5 – Radiation dose (kGy) required to achieve a given SAL for an average bioburden ≥ 1.0 having the standard distribution of resistances.

[12] See ISO 11737-1: Sterilization of medical devices – Microbiological methods – sections 3.3, 7.2(b) and C.2.

Examples of how to determine the alert (warning) and action levels are provided by Winters et al. (see footnote to section 6.2 of this appendix).

7. Product bioburden process control

UNFPA recommends that product bioburden be measured on every lot of product prior to sterilization.

When using the recommended sterilization dose of 25 kGy, ISO 11137-1 states that product is tested for bioburden prior to sterilization at least every three months (Clause 12.1.2.2). If the interval between manufacturing of batches is greater than three months, then every batch must be bioburden tested (Clause 12.1.2.4).

7.1 Existence of outliers in product bioburden data

The existence of bioburden outliers should be considered and it is recommended that these are investigated before acceptance for inclusion in or exclusion from the product bioburden data. If the investigation identifies a problem with the process, this should be investigated and remedied before bioburden limits are set.

7.2 Purpose and use of alert (warning) levels

The main purpose of the alert level is to trigger investigation of the process so that control can be maintained without necessarily triggering corrective actions or raising issues of product conformity and acceptability for terminal sterilization. The levels may be significantly lower than the limits set in the applicable standard. They are provided to indicate the possibility of significant changes in the process. The purpose of alert (warning) levels is to enable the process control to be effective in preventing excursions of product bioburden that could potentially compromise the defined level of sterility assurance.

7.3 Purpose of action levels

The main purpose of the action level is to trigger corrective actions and raise issues of product conformity and acceptability for terminal sterilization. The purpose of the action level is to address the risk of releasing a non-sterile product.

For example, the limits given in the radiation standard[13] and the statistic of 10 times the expected bioburden level are directly related to the risk of product being non-sterile. Product bioburden results at or above 10 times the expected value limit but well below the limits in the standard must be investigated so

[13] See ISO 11137-2: Sterilization of health care products – Radiation, Table 5 – Radiation dose (kGy).

that the source of contamination can be identified and assessed. Depending on the source, type and distribution of bioburden, terminal sterilization at the established dose might still be acceptable subject to satisfactory verification that the radiation dose is still effective.

8. Parametric release

Sterility assurance by post-sterilization sterility testing of a sample of sterilized product is completely inadequate. UNFPA therefore requires parametric release based on a documented procedure according to The European Agency for the Evaluation of Medicinal Products.[14]

[14] Committee for Medicinal Products for Human Use (CHMP) – Guideline on Real Time Release Testing (formerly Guideline on Parametric Release). EMA/CHMP/ QWP/811210/2009-Rev1 (2012).

Appendix 3

Guidance for stability studies

1. Introduction and WHO/UNFPA requirements

Stability studies are performed on medical devices to estimate their shelf-life under specified storage conditions and permit product expiry dates to be calculated. When conducting stability studies, it is essential that fully finished products in their final packaging are used. Changes in packaging can have an impact on the shelf-life of many products. Terminally sterilized products must have been subjected to the full sterilization cycle. Radiation sterilized products must have been subjected to the maximum dose for the maximum period of time specified in the standard operating procedures for the product.

In the case of copper-bearing intrauterine devices (IUDs), manufactures must specify the "insert before date". This is the date from the time of manufacture to the end of the shelf-life period derived from stability studies. This confirms that the IUDs will continue to meet all the requirements of this World Health Organization (WHO)/United Nations Population Fund (UNFPA) TCu380A IUD technical specification up to the time of insertion.

A product's shelf-life can be estimated using accelerated studies but, for most products, it is necessary to confirm the results of accelerated studies by conducting long-term stability studies at the intended storage temperature. These studies are normally called real-time stability studies. The storage conditions for real-time studies have to be determined in advance. The concepts of mean kinetic temperature and world climatic zones, which are discussed in the next section, are extremely useful aids for selecting the storage conditions for real-time studies. Both real-time and accelerated stability studies must be carried out on a minimum of three lots.

2. Real-time stability studies

Real-time stability studies are conducted under a fixed set of storage conditions for the full lifetime of the product. Samples are tested periodically, usually annually, to confirm that they remain in conformance with the specification. Many characteristics of a product will not change during the storage period, whereas other will. It is therefore necessary to identify the critical performance measurements that might change and that could, in the event of any change, affect the safety and effectiveness of the product. These critical performance measurements need to be monitored during the stability study to ensure that they remain within the specified limit.

For the TCu380A IUD, the critical performance requirements listed below have been identified:

- T frame breaking strength
- thread tensile strength
- viscoelastic recovery (memory)
- collar retention force.

Since IUDs are sterile devices, it is also essential to monitor the integrity of the individual pouches during real-time stability studies. Any failure of the pouch could compromise the sterility of the device.

The critical individual pouch measurements that need to be monitored are:

- individual pouch integrity
- individual pouch peel strength.

These requirements have to be monitored on a periodic basis during the real-time stability study to assess if significant changes are occurring as the study progresses. If these properties deteriorate to a level where the product may no longer meet specification, the shelf-life limit may have been reached.

An extremely useful concept used in the pharmaceutical sector for determining the temperature at which real-time stability studies should be conducted is the mean kinetic temperature (*1*). This is a single derived temperature that, if maintained over a defined period, affords the same thermal challenge to a pharmaceutical product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature for a particular storage location can be calculated given knowledge of periodic temperature variations. Many modern temperature data loggers can automatically measure the mean kinetic temperature over a period of time.

Another extremely useful concept from the pharmaceutical sector for determining the conditions for conducting real-time stability studies is the division of the world into a set of four climatic zones, each with its own defined mean kinetic temperature and average humidity (*1*). Based on these zones, WHO and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[15] have developed guidelines for conducting long-term (that is, real-time) stability studies for pharmaceutical

[15] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was originally known as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (created in April 1990; name change in 2015).

products (*2*, *3*). These recommendations have been adopted by WHO/UNFPA for conducting stability studies on IUDs.

IUDs are intended for distribution and storage on a worldwide basis, with most of the public sector supply going to hot or tropical countries. Real-time stability studies should be done under the conditions specified for climatic zones III (hot and dry) and IV (hot and humid), both of which have mean kinetic temperatures of 30 °C. For these reasons, 30 °C has been set as the standard temperature for all stability studies on IUDs intended for WHO/UNFPA prequalification.

In 2006, ICH withdrew the Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV because some countries wanted larger safety margins for these zones. The decision was taken to leave the definition of storage conditions for WHO climatic zones III and IV to the respective regions and WHO. As a consequence, the specified relative humidity for climatic zone IV is now determined by local and regional regulatory authorities. Many have adopted (75 ± 5) % relative humidity rather than the previously specified (65 ± 5) % relative humidity specified in ICH QF1 for climatic zone IV. More information on these changes is given in reference (3). This reference includes a list of countries that have opted to specify (75 ± 5) % relative humidity conditions. Although relative humidity is unlikely to have any effect on the properties of the IUD directly, pouch seal integrity could be affected depending on the type of polymers used to form the seal. For this reason, any new stability studies shall be conducted at (75 ± 5) % relative humidity. Studies at (75 ± 5) % relative humidity shall be initiated upon publication of this revised technical specification and guidance document. Data on studies conducted at 65% relative humidity will remain acceptable until these studies have been completed.

The real-time ageing study shall be commenced at the same time as any accelerated studies, using samples drawn from the same production lots.

The results from the real-time study shall be submitted on its conclusion to interested parties, including UNFPA, to confirm the shelf-life estimate from the accelerated ageing study. Based on real-time studies, IUD manufactures may claim an "insert before date" up to seven years from the date of manufacture.

3. Accelerated stability studies

Accelerated ageing studies are usually carried out at elevated temperatures to force the various chemical processes that are responsible for changes to the product to proceed at a faster rate. Other accelerating factors such as light, humidity and pH can also be used.

Shelf-life estimates made at higher temperatures have to be related back to the standard storage temperature of 30 °C that has been set for real-time studies. This can often be done using the Arrhenius equation, which describes

the relationship between the rate of chemical reactions and temperature (*4*). The Arrhenius relationship, however, does not apply in all cases. This is why it is still essential to use real-time studies to verify shelf-life estimates from accelerated studies.

The Arrhenius equation is usually written as:

$$kT = A \cdot e^{-Ea/RT}$$

Where:

A = constant (min–1)

E_a = activation energy (J/mole)

R = universal gas constant (8.314 J • mol–1 • K–1)

T = absolute temperature (K)

k_T = rate constant for the degradation process (min–1).

An alternate way of expressing the Arrhenius equation is:

$$\ln(k_T) = \ln(A–E_a/RT).$$

The increase in the rate of a chemical process with temperature, as described by the Arrhenius equation, is characterized by a parameter called activation energy E_a. A literature search for the activation energy of polyethylene oxidation during the induction phase, which is considered to be the most likely degradation process that could occur with the TCu380A IUD, found values ranging from 114 kilojoules (kJ)/mole to over 200 kJ/mole.[16] These activation energies would lead to the rate of oxidation increasing by at least 4.7-fold (for an activation energy of 114 kJ/mole) to over 15-fold (for activation energies over 200 kJ/mole) as the temperature is raised from 20 °C to 30 °C.

The ageing periods required at different elevated temperatures to provide an equivalent degree of ageing as storage for five years at 30 °C have been estimated using the Arrhenius relationship and an assumed activation energy of 78 kJ/mole. If samples of a product that have been aged at the specified elevated temperatures for these time periods remain within specification, then it is highly probable that the shelf-life of the product exceeds five years at 30 °C. Choosing a relatively low activation energy of 78 kJ/mole to calculate the ageing periods at the different temperatures means that the estimated shelf-life will be conservative.

[16] The search was conducted using the search terms "activation energy", "polyethylene" and "oxidation", using Google Scholar. Only peer-reviewed papers and publications from recognized academic institutions were included in the review.

In practice, therefore, the shelf-life is likely to be longer than five years at 30 °C if products remain in conformance with the specification at the end of each of the recommended ageing periods and the maximum permitted changes are not exceeded. A full Arrhenius analysis should allow the actual shelf-life to be estimated (see Appendix 4 for an example of the application of the Arrhenius equation to accelerated ageing data for guidance).

Given the intrinsic uncertainties inherent in the interpretation of accelerated stability studies, the latest "insert before date" has been restricted to no later than five years from the date of manufacture. For a seven-year "insert before" period to be accepted, real-time stability studies are required.

It can be shown that the time required for the physical properties to deteriorate to a specific threshold value is inversely proportional to the rate constant k_T. Plotting the natural log of the times required at different temperatures for a property, such as frame strength, to fall to the threshold value against the reciprocal of those temperatures (expressed in Kelvin) should therefore result in a straight line if the degradation process follows the Arrhenius relationship. The slope of the straight line will be equal to E_a/RT.

To facilitate a full Arrhenius analysis, the times required at different temperatures for the physical property that is being monitored to deteriorate to a specific threshold value are determined. The threshold value may be the limit for the property being tested at which the IUD will become nonconforming. Alternatively, it may be an arbitrary limit that is set for convenience, such as a fall in strength by 25%. The threshold limit should be chosen such that the time to reach this limit can be determined with a reasonably reliable degree of statistical confidence. It should also be no greater that the maximum permitted change beyond which the product is expected to become nonconforming.

The method recommended in this section for conducting stability studies is based on ISO 11346:2004: Rubber, vulcanized or thermoplastic – Estimation of lifetime and maximum temperature of use.

4. Method of conducting stability studies

4.1 Use of standard reference product

If possible, a reference product with an established shelf-life should be included in the stability study. If a change in specification, raw materials or manufacturing process has been made, then samples of the original product can be used as the reference product. In some cases, it may be appropriate to use a competitive product as a reference sample. All the reference samples shall be from the same lot and shall be within six months of the stated manufacturing date.

4.2 Equipment

ISO 188:2007: Rubber, vulcanized or thermoplastic – Accelerated ageing and heat resistance tests specifies that two methods can be used for conducting stability studies:

- method A: air-oven method using a cell-type oven or cabinet with low air speed and a ventilation of 3 to 10 changes per hour;
- method B: air-oven method using an oven or cabinet with forced air circulation by means of a fan and a ventilation of 3 to 10 changes per hour.

Ovens or conditioning cabinets should therefore comply with one of these requirements. Whichever type of oven or cabinet is used, it must be consistent from experiment to experiment and within an experiment.

The hygrometer used to monitor the relative humidity shall be accurate to ± 2% relative humidity. The calibration of many types of hygrometer can drift significantly over time. It is essential that a calibrated instrument is used. A psychrometer may be used either for direct measurement of relative humidity or as a reference standard for the hygrometer. If a psychrometer is used, the instrument must be calibrated (see reference (*5*) for general advice on the selection and calibration of hygrometers).

4.3 Test items

Samples from normal production made using normal production equipment and processes (including packaging equipment) that meet all specification requirements and are within six months of the date of manufacture and sterilization shall be used in testing. Samples shall be in standard packaging.

4.4 Use of retained samples

It may be of value to consider using any retained samples that have already been stored for a significant period. These could allow comparison of real-time and accelerated ageing results. Additionally, including such samples would allow evaluation of the effect of accelerated ageing on samples that have already undergone some real-time ageing.

4.5 Test sample size

It is strongly recommended that additional samples be included in the study to allow for retests and mistakes. When estimating the number of additional samples, the manufacturer should allow for at least one retest at each temperature, using a sample size with an acceptance number of one or more.

4.6 Example test protocol

Table 7 lists a set of ageing periods at different temperatures that can be considered equivalent to storage at 30 °C for periods of one to seven years in annual increments. These periods were calculated using the Arrhenius relationship and assume an activation energy of 78 kJ/mole. The times have been rounded up to the nearest week. The relative humidity (RH) for the accelerated ageing and real-time studies shall be maintained at (75 ± 5) % RH. At elevated temperatures, a humidity of at least (75 ± 5) % RH at the ageing temperature shall be maintained.

Table 7
Ageing periods by temperature (critical individual pouch measurements)

Temperature	Ageing periods (weeks) at specified temperature (tests to be conducted)						
80 °C[a]	1	–	2	–	4	–	5
70 °C	2	3	5	6	8	9	10
60 °C	4	7	10	13	17	20	23
50 °C	8	16	23	31	39	46	54
40 °C	20	39	59	78	97	117	136
Real-time study at 30 °C	52	104	156	208	260	312	364
Shelf-life supported (years)	1	2	3	4	5	6	7

[a] Due to the very high degree of acceleration seen at 80 °C, the number of time points has been reduced.

It is important to note that the ageing periods in Table 7 are estimates. They should be confirmed as part of the accelerated stability study. Appropriate combinations of these times and temperatures can be selected when designing stability studies. For example, by measuring how the critical properties of the IUD change over time at a minimum of three different temperatures, a full Arrhenius analysis of the data can be made, as described in section 3 above of this appendix. Critical performance measurements (T frame breaking strength, thread tensile strength, memory and collar retention force) should be measured at each time interval for the specific temperatures selected. In order to be able to use the Arrhenius method for analysing the data, it is important to continue the ageing periods at the selected temperatures until the properties being measured have changed by the preselected threshold amount (different thresholds can be used for different properties if necessary) or until the maximum period at the ageing temperature has been reached. It is only necessary, however, to measure the

critical individual pouch measurements (that is, pouch integrity and pouch peel strengths) at the time periods for the selected temperatures that are equivalent to five years at 30 °C to confirm a five-year shelf-life and seven years at 30 °C to confirm a seven-year shelf-life.

Table 7 also includes the recommended annual time intervals and tests required for the real-time study at 30 °C. Critical performance measurements and critical individual pouch measurements should be completed at each time point in the real-time study.

Once a full Arrhenius analysis has been conducted, the time periods can be recalculated based on the actual activation energy derived from the Arrhenius relationship. This makes it easier to carry out further stability tests if necessary; for example, following changes to the product, manufacturing process or packaging, a further Arrhenius analysis is unnecessary and a single temperature can be selected from the amended table to verify shelf-life claims.

4.7 Measurements

Strength measurements are carried out using the amended "arms-up" method outlined in the technical specification. The IUD frame in the arms-up configuration and the thread (suture) shall be tested independently. Elongation at break shall be recorded and reported.

Results shall be produced from a portion of the original sample immediately before ageing to establish the baseline from which changes are measured.

Biocompatibility and sterility measurements should not be repeated.

4.8 Significant change

All test results shall be in conformance with this revised WHO/UNFPA TCu380A IUD technical specification using the sampling plan specified.

Any results failing to comply with the specification or showing 25% or greater change from the initial values shall be deemed significant.

A 25% or greater fall in IUD frame strength, thread strength or pouch peel strength shall be taken as an indication that the acceptable shelf-life of the product and individual pouch has been exceeded, even if these properties comply with the specification.

4.9 Tarnishing

Tarnishing can be expected. If it occurs, it should be noted. There is no evidence that tarnishing affects the shelf-life or performance of the product but excessive tarnishing could cause the product to be rejected by the purchaser or end user.

5. Test results reporting

5.1 Test results

Results shall be reported for the real-time and accelerated ageing product at all the temperatures and times specified. Sample sizes, environmental and ageing conditions, equipment and test methods shall all be referenced.

Records shall be included on any features of note, such as effects on the packaging and product, whether or not reflected in the results; and any testing conditions or events, whether or not it is believed that they affected the results.

The results shall be evaluated statistically and reported in terms of the estimated shelf-life, with associated estimates of uncertainty.

5.2 Sample estimates

Sample sizes shall be equal to or greater than 13. The sample mean and standard deviation shall be reported as well as the number of nonconforming samples.

6. Estimating the shelf-life

Depending upon the outcome of the stability study, different procedures can be used to estimate the shelf-life of the product.

6.1 No significant changes are seen in the critical performance measurements at the maximum recommended storage time at each ageing temperature

In this case, it will not be possible to estimate the actual shelf-life of the product, but the maximum time periods have been selected on a very conservative basis to provide a high level of confidence that the shelf-life is in excess of five years at 30 °C if no changes are seen during the accelerated study. If there are no significant changes, it can be concluded with a high degree of confidence that the shelf-life is in excess of five years.

6.2 Significant changes are seen in the critical performance measurements at three or more ageing temperatures, but these are below 25%

As long as significant changes are seen at three or more of the temperatures chosen for the stability study, then a full Arrhenius analysis can be carried out as described in ISO 11346. For full details on how to do this, refer to ISO 11346. Briefly, the natural logarithms of the times required at each temperature for the critical performance measures to deteriorate to the selected threshold value are plotted against the reciprocals of each temperature (expressed in Kelvin). Appropriate extrapolation methods may be used at each temperature to determine the time to reach the threshold values.

If a linear Arrhenius plot is obtained, then it will be possible to estimate the shelf-life at 30 °C with a reasonable degree of confidence by determining the time required for the critical performance measures to decrease by 25% or reach the specified threshold values, whichever occurs earlier. It may be necessary to estimate these times by extrapolation (projecting the curve or line beyond the limits of the data) or interpolation (projecting between data points).

If the Arrhenius plot is not linear, then consider using the procedure associated with the Williams-Landel-Ferry time–temperature superposition equation as described in ISO 11346 (assistance will probably be required to do this analysis).

6.3 A critical performance measurement deteriorates by 25% or more within the time periods specified in Table 7

If a critical performance measurement does not comply with the specification or falls below 25% of the initial value before the maximum duration in weeks at any given temperature, then the shelf-life of the product may be less than five years at 30 °C. An Arrhenius plot should be constructed using 25% as the threshold limit for deterioration and an appropriate shelf-life calculated. In some cases, it is expected that the estimated shelf-life will be less than five years at 30 °C, but this depends upon the actual activation energy estimated from the Arrhenius plot and whether the plot is linear. It is possible that some degradation processes may occur only at the higher temperatures used in the study and, therefore, not contribute to deterioration of the product under normal storage conditions. If a very marked temperature-dependent effect is observed, then validation of the provisional shelf-life estimate by a real-time study becomes particularly important.

References

1. Grimm, W. Storage conditions for stability testing in the EC, Japan and USA: the most important market for drug products. Drug Development and Industrial Pharmacy. 1993;19(20):2795–830.
2. ICH Q1A (R2): Stability testing of new drug substances and products. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (formerly International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use); 2003.
3. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-third report. WHO Technical Report Series No. 953, Annex 2. Geneva: World Health Organization; 2009.
4. Arrhenius S. Über die Reaktionsgeschwindigkeit bei der Inversion von Rohrzucker durch Säuren [About the rate of reaction in the inversion of cane sugar by acids]. Zeitschrift für Physikalische Chemie. 1889;4:226 and 1899;31:187.
5. World Meteorological Organization. Guide to meteorological instruments and methods of observation, seventh edition. WMO; 2008.

Applicable standards

ASTM F1980-07: Standard guide for accelerated ageing of sterile barrier systems for medical devices.

EN 455-4: Medical gloves for single use – Part 4: Requirements and testing for shelf-life determination.

ISO 188: Rubber, vulcanized or thermoplastic – Accelerated ageing and heat resistance tests.

ISO 7439: Copper-bearing intrauterine devices.

ISO 10012: Measurement management systems – Requirements for measurement processes and measuring equipment.

ISO 11346: Rubber, vulcanized or thermoplastic – Estimation of life-time and maximum temperature of use.

ISO 13485: Medical devices – Quality management systems – Requirements for regulatory purposes.

WHO Working document QAS/06.179 (restricted). Stability testing of active substances and pharmaceutical products.

Appendix 4

Application of the Arrhenius equation to accelerated ageing data

1. Background

This annex provides an example of how to conduct an Arrhenius-based analysis of stability data for a medical device. The data do not specifically apply to the TCu380A intrauterine device (IUD) and are used as an example only.

For many chemical reactions, the rate at which the reaction occurs varies with temperature according to the Arrhenius equation:

$$k_T = Ae^{-Ea/RT} \quad (1)$$

Where A is a constant, Ea is the activation energy, R is the gas constant (8.31432 J/°K/mole) and T is the absolute temperature. kT is the rate constant for the particular chemical reaction concerned at temperature T. It can be shown that the time required for a reaction to reach a specified threshold, say 20% completion, is inversely proportional to the rate constant k_T. This applies whatever the order of the reaction is. The Arrhenius equation can therefore be rewritten in terms of the time required to reach a specified threshold, $t_{(x\%)}$, as:

$$C/t_{(x\%)} = Ae^{-Ea/RT}, \quad (2)$$

where C is a constant. Taking logs of both sides and rearranging equation (2) gives us equation (3):

$$\ln(t_{(x\%)}) = Ea/RT - \ln(A/C) \quad (3)$$

If it is assumed that there is a direct relationship between the underlying chemical changes and the observed change in the physical property being observed, then equation (3) also models the time required for that physical property to reach a specified threshold.

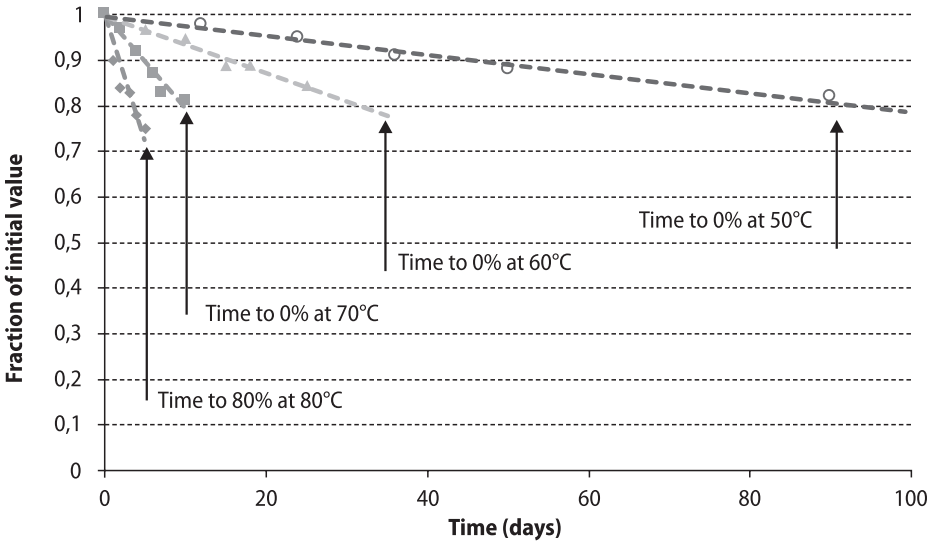
If the Arrhenius equation is applicable, then it follows from equation (3) that a straight line will be obtained by plotting $\ln(t_{(x\%)})$ against 1/T(°K). Assuming that a straight line is obtained, then it is very easy to extrapolate the line and determine time required for the predetermined degree of change to occur at the target storage temperature. The activation energy Ea can be readily calculated form the slope of the line, recognizing that:

$$\text{Slope} = Ea/RT \quad (4)$$

2. Estimating the time required to reach a specified threshold value

The first stage in preparing an Arrhenius plot is to determine how long it takes at each temperature for the physical property under investigation to reach a predetermined threshold. Ideally, the threshold value should represent the maximum change that can be tolerated before the medical device is at risk of failing the specification. This may not always be possible, particularly at lower temperatures and with stable materials. The difference between initial and threshold values should nevertheless be sufficiently large compared to the background variability to allow the time to be estimated accurately. It may be necessary to extrapolate data obtained at lower ageing temperatures in order to determine the time to reach the threshold value. Fig. 8. illustrates how this is done, assuming the threshold limit is set at 80% of the initial value. In this particular example, linear extrapolation of the 50 °C data was required to reach the 80% threshold.

Fig. 8
Estimating the time to 80% of initial value



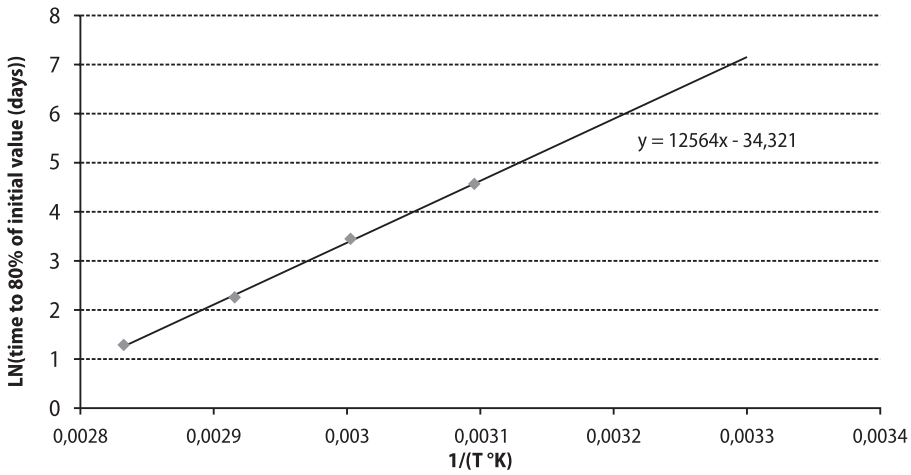
Note: Estimating the time to reach a specified threshold is often easier if linear regression methods can be used to fit a straight line through the data. In order to do this, it may be necessary to apply an appropriate transformation to the data first. Many chemical processes follow first-order kinetics, such as, the rate of change is proportional to the instantaneous value of the variable under consideration. If the rate of change of a specific property follows first-order kinetics, then a straight line can be obtained by plotting the natural log (ln) of the property against time.

Note: In some ageing processes, sudden changes in the rate of degradation can occur, for example when all the antioxidant is consumed. If it is necessary to extrapolate data to determine the time required to reach the specified threshold, then consideration should be given to the possibility of such effects.

3. Constructing the Arrhenius plot and estimating the activation energy

The Arrhenius plot is constructed by plotting the natural logs of the times required for the property under investigation to reach the specified threshold value (ln(tx%)) against the reciprocal of the absolute temperature. A typical plot is shown in Fig. 9.

Fig. 9
Arrhenius plot based on time to reach of 80% of initial value



Note: The time estimated for the property under investigation to fall to 80% from Fig. 2 is 1267 days at 30 °C. The activation energy is calculated as 104.5 kJ/mole.

In some cases, the Arrhenius plots may not be linear. Several approaches to the analysis of non-linear Arrhenius-type plots have been explored and are published in the scientific literature. It must be emphasized that any attempt to extrapolate shelf-life estimates from non-linear Arrhenius plots carries a high level of risk, and manufacturers should be conservative about any estimates made under such conditions.

Typically, activation energies for many chemical reactions average 83 kJ/mole,[17] although the actual range found in practice varies widely. Published values for the activation energies associated with thermal or oxidative degradation of the material being used may be available in the scientific literature.

[17] Kennon L. Use of models in determining chemical pharmaceutical stability. J Pharm Sci. 1964:53:815–8.