

# The TCu380A Intrauterine Contraceptive Device (IUD):

Specification, Prequalification and  
Guidelines for Procurement, 2010



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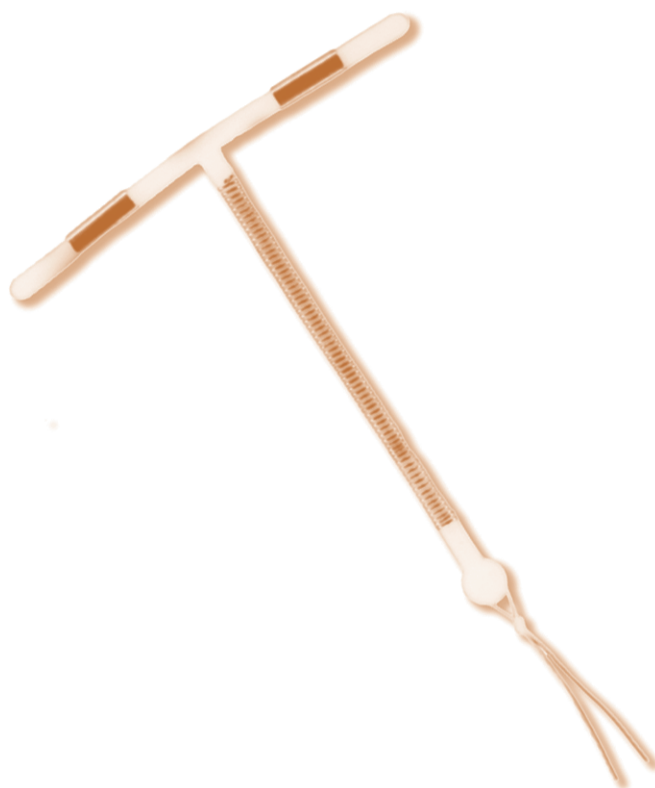
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# The TCu380A Intrauterine Contraceptive Device (IUD):

Specification, Prequalification and Guidelines for Procurement, 2010



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THE SCIENCE OF  
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Family and Community Health  
World Health Organization

## **The TCu380A Intrauterine Contraceptive Device (IUD): Specification, Prequalification and Guidelines for Procurement, 2010**

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## INTRODUCTION

The Copper T 380A intrauterine device (TCu380A IUD) is a popular, safe and very effective contraceptive (1). Once the device is inserted, the user benefits from up to 12 years of effective protection against unintended pregnancy. The recommended years of use can vary according to the guidelines and policies of a country. Health care providers should follow programme guidelines as to when the device should be removed. The method is immediately reversible upon removal.

The device does not interrupt sexual intercourse because it does not require any action on the part of the user. In addition, because the IUD is inserted in a woman's uterus by a specially trained health care provider, it is unlikely to fail due to the user's mistake or negligence, a potential problem with many other contraceptive methods. IUDs are relatively inexpensive to manufacture and are widely available.

In 2007 there were an estimated 162,680,000 women using IUDs. This represented 23% of all users of contraceptives and 14% of all women ages 15–49 who were married or in union (2).

### 1.1 Safety and efficacy

The TCu380A IUD has been shown to be an effective, safe, long-term contraceptive device. Studies show that the copper-bearing IUD is nearly as effective as male or female sterilization. The TCu380A is available in over 100 countries, but it is still often underutilized. One reason is lack of information or misinformation on the part of both clients and providers.

The WHO guidelines on contraceptive use, the *Medical Eligibility Criteria for Contraceptive Use* (3) and *Selected Practice Recommendations for Contraceptive Use* (4) provide guidance on when a copper-bearing IUD can be inserted. The *Medical Eligibility Criteria* identifies few restrictions on use based on either an individual's characteristics or known medical conditions. In fact, the IUD is safe and suitable for nearly all women including adolescents and women over 40, women who have just had an abortion or miscarriage as long as there is no infection, women who are breastfeeding, women who have had pelvic inflammatory disease and are currently free from infection, and women who are infected with HIV on antiretroviral therapy and clinically well. If, however, a woman has a very high individual risk of having gonorrhoea or chlamydia at the time of insertion, or if she has AIDS and is not on antiretroviral therapy and not clinically well, she should not have an IUD inserted.

As with most contraceptive methods, there is some risk of side effects. These include the possibility of longer, heavier, and sometimes painful menstrual periods, especially during the first three to six months of use.

There are very few serious health risks associated with using the IUD. Uncommonly heavier menstrual bleeding due to a copper-bearing IUD may contribute to anaemia if the woman already has low iron stores before insertion. Even rarer is the risk of pelvic inflammatory disease associated with an ongoing gonorrhoeal or chlamydial infection at the time of IUD insertion.

Complications of IUD insertion are uncommon. During insertion there is a small risk of perforation of the wall of the uterus by the IUD or the instrument used to insert it.

Occasionally, an IUD is expelled. This is usually harmless unless a woman does not notice it and becomes pregnant.

There are quite a few misperceptions regarding the use of IUDs that have been clarified in the WHO guidelines on contraceptive use (2,3) and in WHO's *Family Planning: A Global Handbook for Providers* (1). Such clarifications include these: Use of an IUD rarely leads to pelvic inflammatory disease (PID); IUDs do not increase the risk of contracting sexually transmitted infections (STIs) including human immunodeficiency virus (HIV), which causes AIDS; IUDs do not make a woman infertile; they do not cause birth defects; they do not cause cancer; they do

not move to the heart or brain; and they do not cause discomfort or pain for the woman during sex. Also, IUDs substantially reduce the risk of ectopic pregnancy compared with the risk of using no contraception.

The copper-bearing IUD is an appropriate contraceptive for the postpartum period. A recommendation in the 2008 update of the WHO *Selected Practice Recommendations for Contraceptive Use* (4) states that a woman can have a copper-bearing IUD inserted up to 48 hours after delivery, including immediately after delivery of the placenta. If the delivery is by caesarean section, a copper-bearing IUD can be placed after delivery of the placenta, before closing the uterus.

If the copper-bearing IUD is not inserted within 48 hours after delivery, then a woman can have the IUD inserted at four weeks postpartum or thereafter, provided her menstrual cycle has returned. If it has not returned, the IUD can be inserted if it can be determined that the woman is not pregnant.

IUDs do not protect against STIs, including HIV. The correct and consistent use of condoms is recommended either alone, or with another contraceptive method such as an IUD, for effective STI/HIV prevention.

Copper-bearing IUDs work primarily by causing chemical changes that prevent fertilization. Studies show that the copper IUD effectively interrupts the reproductive process before implantation and pregnancy, suggesting that it does not act by initiating an abortion, as has sometimes been suggested.

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.

## **1.2 Copper TCU380A IUD recommended for bulk procurement**

Copper-bearing IUDs come in a variety of shapes. The one recommended by WHO for bulk procurement is the TCU380A. This IUD is T-shaped. The horizontal arms of the T keep the IUD in place within the uterus. Copper-bearing IUDs usually consist of a plastic body to which copper is attached. In the earlier models the copper was wound around the vertical stem only, but in more recent designs copper sleeves have been added to the horizontal arms to increase the surface area of copper and thus improve efficacy. Sometimes the copper wire contains a silver core, which is claimed to delay fragmentation of the wire and so increase the lifespan of the device.

In 2006 a Cochrane Review of copper-bearing IUDs was published. This review was prepared by the Geneva Foundation for Medical Education and Research, the Leiden University Medical Centre, the Westminster Primary Care Trust London and the WHO Department of Reproductive Health and Research. The review was updated in 2007 (5) and published as an article in *Contraception* (6). The purpose of the systematic review was to compare different copper-bearing IUDs for their effectiveness and side effects, including evidence on whether there is an association between IUD use and pelvic inflammatory disease.

Following publication of the Cochrane Review, WHO and UNFPA convened an IUD Technical Review Committee Meeting to consider its findings and their implications for public health. Attending the meeting were international experts and researchers in the field of IUDs together with the convenor of the International Organization for Standardization Technical Committee 157, Working Group 3 (ISO/TC/157 WG3), which is the international standards technical committee working group responsible for developing the international standard for copper-bearing IUDs, *ISO 7439*,<sup>1</sup> and other representatives of ISO/TC/157 (the international

<sup>1</sup> Normative references: For undated references to international standards, the latest edition of the reference document, including any amendments and corrigenda, applies. For dated references to international standards, only the edition cited applies.

standards technical committee responsible for non-systemic contraceptives and STI barrier prophylactics), the authors of the Cochrane Review and representatives from WHO Secretariat. The meeting took place on 19–20 September 2006 at WHO Headquarters in Geneva, Switzerland.

The IUD Technical Review Committee reached consensus on a number of recommendations concerning the efficacy and safety of IUDs, many of which related to the international standard for copper-bearing IUDs, *ISO 7439*. The relevant recommendations were communicated to the ISO/TC/157/WG3. Further details of the conclusions reached by the Technical Review Committee are given in Annex I: Technical Basis Paper: Revision of the TCu380A IUD Specification.

The IUD Technical Review Committee recommended that:

1. The TCu380A IUD should be the preferred device for public-sector procurement on the basis of its efficacy, safety and long history of use.
2. The specification for the TCu380A IUD, originally prepared by the Population Council in 1984, should be updated to reflect general changes in medical device manufacturing practice, material availability and specification writing that have occurred since the publication of the original specification.

### **1.3 Prequalification**

The TCu380A IUD is widely distributed by various public-sector agencies, and the decision was taken by WHO and UNFPA to introduce a prequalification scheme for TCu380A IUD manufacturers that is harmonized with the WHO Prequalification Scheme for Essential Medicines. The aim of the WHO/UNFPA Prequalification Scheme is to determine whether the applicant/manufacturing site meets the minimum requirements detailed in the relevant ISO standards and *WHO/UNFPA Specification* in respect of product quality and safety, production and quality management, regulatory approvals, and capacity of production.

The WHO/UNFPA Prequalification Scheme involves the following key activities:

- evaluation of documents submitted in response to an invitation to provide an Expression of Interest (EOI)
- manufacturing site inspection
- product testing
- review of testing and inspection reports to inform a decision about the acceptability of each applicant
- publication and the periodic updating of a list of prequalified products and manufacturing sites on WHO/UNFPA web sites.

The prequalification procedure was submitted to the 42nd WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2007. The expert committee approved in principle the procedure, subject to external review. The procedure was published in May 2008 as WHO Technical Report Series 948 (7).

### **1.4 Preparation of this document**

In response to these recommendations, a series of IUD Technical Review Committee Meetings were held between November 2006 and August 2008 to develop an amended specification for the TCu380A IUD and guidelines for the prequalification of IUD manufacturers under the WHO/UNFPA Prequalification Scheme. These meetings were attended by experts in the manufacture of IUDs, representatives of various public-sector procurement agencies and organizations, representatives from WHO and UNFPA, experts in drafting medical



device specifications and standards, and experts in medical device quality management systems and audits. Extensive consultations were conducted with IUD manufacturers to ensure that the revised specification reflects current manufacturing practice. In addition, from August 2008 to April 2010, WHO commissioned a team of experts to investigate the *in utero* ageing behaviour of TCU380A IUDs. Since the materials, manufacturing process and methods of sterilization have changed over the last 25 years, it was considered important to determine if new tests and requirements were needed to ensure the integrity of the IUD during the ageing process. Refer to Annex VI for a protocol for assessing ageing behaviour prior to the availability of real-time data.

In January 2010 a workshop was held for all manufacturers of TCU380A IUDs to discuss the conclusions and recommendations emerging from this research and the final draft of the revised specification and prequalification process. Consensus was reached with all parties during this workshop, and the document was then sent for external review prior to publication.

### **1.5 Purpose of this document**

This document is designed to provide manufacturers, procurement agencies and programme managers with up-to-date information about the revised *WHO/UNFPA TCU380A IUD Specification*. This includes a justification for the changes that have been made, the detailed specification, a description of the process for its development, and operational guidelines for the WHO/UNFPA Prequalification Scheme and the procurement process for the TCU380A IUD.

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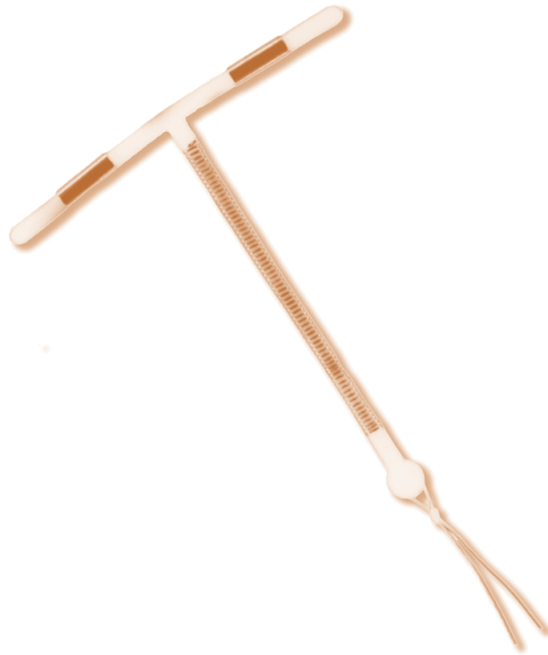
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## **SECTION ONE**

### **WHO/UNFPA TCU380A INTRAUTERINE DEVICE (IUD) SPECIFICATION, 2010**



## **CHAPTER 1**

### **WHO/UNFPA TCu380A Intrauterine Device (IUD) Specification, 2010**



## SECTION ONE

# CHAPTER 1: WHO/UNFPA TCU380A INTRAUTERINE DEVICE (IUD) SPECIFICATION, 2010

## 1 General description

The TCU380A IUD consists of a T-shaped frame made from low-density polyethylene with barium sulphate added for X-ray opacity. The device is 32 mm wide and 36 mm long, with a plastic ball at the bottom of the vertical stem to guard against cervical penetration. A small hole may be located on the vertical stem near to its junction with the horizontal arms to act as an anchor for the copper wire. The IUD has solid copper collars on each of its two horizontal arms. Each of these collars has a surface area of 35 mm<sup>2</sup>. Copper wire with a surface area of 310 mm<sup>2</sup> is wound tightly around the vertical stem, giving a total surface area of 380 mm<sup>2</sup> 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.

It is recommended that all biological safety tests in accordance with *ISO 10993* parts 1, 3, 5, 10 and 11 be conducted by accredited laboratories.

The TCU380A IUD is supplied sterile in a sealed primary pack together with an insertion device consisting of a high-density polyethylene tube, a moveable flange and a rod. The moveable 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. The insertion rod keeps the TCU380A IUD correctly positioned within the uterus while the insertion tube is removed.

Other devices to assist the process of insertion may also be provided, for example, an arm-folding device, a uterine sound, sterile gloves, sterile swabs, etc.

## 2 Materials

The following materials shall be used:

### 2.1 T frame

The T frame shall be made from low-density polyethylene (LDPE), free of stabilizers, having a minimum tensile strength of 13 MPa (*ASTM*

*D638—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 24% USP (United States Pharmacopeia) precipitated barium sulphate with a particle size of 95% less than 10 micron. The compounded polymer (LDPE plus barium sulphate) shall be evaluated for biological safety in accordance with *ISO 10993–1* requirements for mucosal membrane contact devices intended for permanent contact. Specifically, the following testing is required:

- testing for genotoxicity according to *ISO 10993–3*
- testing for cytotoxicity according to *ISO 10993–5*
- testing for irritation and delayed-type hypersensitivity according to *ISO 10993–10*
- testing for subacute and subchronic toxicity according to *ISO 10993–11*.

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.

It has been agreed that manufacturers using the original grade of LDPE specified by the Population Council (DuPont™20) do not need to complete the testing according to *ISO 10993*, as specified above, until December 2012 (two years from the date of publication of this specification). After this date manufacturers must have completed the testing.

### 2.2 Copper wire

The wire shall be made from oxygen-free electronic (OFE) 99.99% pure copper meeting the National Bureau of Standards designation UNS C10100. The diameter of the wire shall be  $(0.255 \pm 0.005)$  mm (30 AWG<sup>1</sup>, 33 ISWG<sup>2</sup>).

<sup>1</sup> American Wire Gauge.

<sup>2</sup> Imperial Standard Wire Gauge.

## 2.3 Copper collars

The copper collars shall be made from oxygen-free electronic (OFE) 99.99% pure copper meeting the National Bureau of Standards designation UNS C10100<sup>3</sup>. The collars shall be manufactured from copper tube half hard temper with internal diameter ( $1.68 \pm 0.025$ ) mm and external diameter ( $2.2 \pm 0.025$ ) mm. The collars shall be ( $5 \pm 0.15$ ) mm in length.

The collars shall be deburred, polished and free from sharp edges, for example, by barrel tumbling.

## 2.4 Thread

The thread shall be a monofilament made from high-density polyethylene (HDPE), free of stabilizers, with sufficient tensile strength to meet the specified thread breaking force requirement of 9.5 Newton. A material with a minimum tensile strength (*ASTM D6380—ISO 527-2*) of 28 MPa is recommended. The thread polymer shall be compounded with 0.4% up to 1.0% by weight USP (EP) rutile titanium dioxide.

The compounded polymer (HDPE plus titanium dioxide) shall be evaluated for biological safety in accordance with *ISO 10993-1* requirements for mucosal membrane contact devices intended for permanent contact. Specifically, the following testing is required:

- testing for genotoxicity according to *ISO 10993-3*
- testing for cytotoxicity according to *ISO 10993-5*
- testing for irritation and delayed-type hypersensitivity according to *ISO 10993-10*
- testing for subacute and subchronic toxicity according to *ISO 10993-11*.

For a specific material it is only necessary to carry out the assessment of biological safety once. The evaluation shall, however, be repeated if there is a significant change to the materials, for example, if the grade or supplier is changed.

The thread diameter shall be ( $0.25 \pm 0.05$ ) mm. When tested according to *ISO 7439*, Clause 7 (clamping the thread only), the peak load at break of the thread shall be greater than 9.5 Newton.

<sup>3</sup> See Annex III: Summary Specification for Copper Purity.

It has been agreed that manufacturers using the original grade of HDPE specified by the Population Council (Philips Marlex 6006) do not need to complete the testing according to *ISO 10993*, as specified above, until December 2012 (two years from the date of publication of this specification). After this date manufacturers must have completed the testing.

## 2.5 Insertion tube

HDPE (high-density polyethylene) food contact grade of internal diameter ( $3.7 \pm 0.1$ ) mm and outside diameter of ( $4.4 \pm 0.1$ ) mm shall be used.

## 2.6 Insertion rod

Food contact grade radiation stable ABS (acrylonitrile-butadiene-styrene polymer) or food contact grade radiation-stabilized polypropylene (PP) with a tip diameter of ( $2.6 \pm 0.2$ ) mm shall be used. Optionally, the insertion rod may be pigmented.

## 2.7 Positioning flange

Polymer with adequate radiation stability to function mechanically post-sterilization shall be used. Optionally, the flange may be pigmented.

## 2.8 Packaging

Packaging materials shall comply with *ISO 11607-1*. Polymer films, preferably continuous, shall be used to reduce the risk of tarnishing the copper.

Tarnishing is a natural phenomenon for copper and does not affect the performance of the IUD. However, significant tarnishing of copper during shelf-life may not be aesthetically acceptable. The use of continuous film packaging, where possible, can reduce the risk of tarnishing.

## 3 Materials testing

Every new LOT (batch)<sup>4</sup> of compounded frame material (LDPE plus barium sulphate) and thread material (HDPE plus titanium dioxide) shall be

<sup>4</sup> The terms “LOT” and “batch” are used interchangeably in the manufacture of IUDs. Both refer to the quantity of IUDs produced in a single manufacturing run using the same batches or lots of raw materials.

subjected to *in vitro* cytotoxicity testing in accordance with *ISO 10993–5 Biological Evaluation of Medical Devices. Part 5. Tests for in vitro Cytotoxicity*.

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*.

The barium sulphate content of the frame material shall be determined according to the relevant clause of *ISO 7439*.

#### 4 Materials storage

The maximum storage period for the frame polymer and the thread is 3 years from the date of manufacture when stored at temperatures under 30 °C and 2 years when stored at temperatures between 30 °C and 35 °C.

Manufacturers have until February 2014 to comply with these requirements.

Provided the tensile strength 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 Newton, then the materials may be used for a further 3 years when stored at temperatures under 30 °C and 2 years when stored at temperatures between 30 °C and 35 °C.

#### 5 Materials processing

The recycling of injection moulded reclaim material for the T frame and the thread is NOT permitted.

#### 6 Dimensions and requirements for finished product

A drawing of the IUD assembly is included in Annex IX.

When tested according to the relevant clause of *ISO 7439*, the dimensions of the finished product after sterilization shall comply with the requirements, as individually specified as follows.

Sampling shall be conducted in accordance with *ISO 2859–1*, Inspection Level S-4 unless otherwise indicated.

Compliance shall be with an AQL (acceptable quality level) of 0.65 unless otherwise indicated.

Manufacturers and testing laboratories may opt to sample in accordance with *ISO 3951–1*, using the same Inspection Level and AQL.

In cases of dispute, sampling according to *ISO 2859–1* shall be used.

In order to use the tables in *ISO 2859–1*, it is necessary for the manufacturer to specify the LOT size.

The manufacturer is responsible for defining the LOT size and ensuring traceability and the use of appropriate sampling in process and product validation.

##### 6.1 T frame dimensions

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 hole must not reduce the breaking strength of the vertical stem below that specified in Clause 7.4, below. The hole may be tapered or dumbbell-shaped, with a maximum diameter of 0.55 mm and placed (2.8 ± 0.15) mm from the intersection of the horizontal arm and vertical stem centrelines [equivalent to (3.6 ± 0.15) mm from top edge of the horizontal arm].

- 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 of maximum diameter 0.80 mm for securing the thread. The hole may be tapered or dumbbell-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 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 done 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 Annex IX.

### 6.2 Thread dimensions

The thread is knotted to form two tails of approximately equal length. The length of each tail shall be 105 to 125 mm.

Compliance for thread length shall be an AQL 1.5.

### 6.3 Copper collars

Collar length:  $(5.0 \pm 0.15)$  mm.

Collar weight:  $(68.7 \pm 3.0)$  mg.

Collar position:  $(5.4 \pm 0.4)$  mm from the ends of the T horizontal arm.

A drawing of the copper collars is included in Annex IX.

### 6.4 Copper wire

The weight of wire on the frame shall be not less than 165 mg and not more than 187 mg.

### 6.5 Copper surface area

The total nominal active copper surface area, wire and collars, shall be  $380 \text{ mm}^2 \pm 10\%$ .

### 6.6 Copper wire winding

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 down to run parallel to 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.

### 6.7 Insertion tube

Length:  $(206 \pm 2)$  mm.

Internal diameter:  $(3.7 \pm 0.1)$  mm.

Outside diameter:  $(4.4 \pm 0.1)$  mm.

### 6.8 Insertion rod

Length:  $(190 \pm 5)$  mm from handle brace to tip.

Diameter at tip:  $(2.6 \pm 0.2)$  mm.

### 6.9 Insertion tube flange

Diameter of central hole:  $(4.1 \pm 0.1)$  mm.

The shape and dimensions of the central hole may be changed to facilitate meeting the specified flange displacement force.

Compliance shall be with an AQL of 1.5.

### 6.10 Other assist components

These are other optional components that the manufacturer may evaluate and choose to include. When considering design and choice of materials for these components, manufacturers shall take into account the function of the devices, the type and duration of exposure to the body and the effect of sterilization by gamma radiation.

## 7 Performance requirements

When tested according to the relevant clause of *ISO 7439* or the specified test method, the performance requirements of the finished product after sterilization shall comply with the requirements specified below.

Sampling shall be in accordance with *ISO 2859-1*, Inspection Level S-4 unless otherwise specified.

Manufacturers and testing laboratories may opt to sample in accordance with *ISO 3951-1*, using the same Inspection Level and AQL.

In cases of dispute, sampling according to *ISO 2859-1* shall be used.



### 7.1 Breaking strength

Sampling shall be in accordance with *ISO 2859-1*, Inspection Level G-1.

Compliance shall be with an AQL of 1.0.

The breaking force of the finished product after sterilization shall be greater than 9.5 Newton when tested according to the relevant clause *ISO 7439*.

The IUD shall be tested with the arms of the T frame bent upwards and clamped parallel to each other at a distance of  $(8 \pm 2)$  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.

Temperature during testing shall be  $23 \pm 2$  °C.

Conditioning, as specified in relevant clause of *ISO 7439:2002* needs to be carried out only in the case of disputes.

An example of a suitable clamp for holding the device is shown in Photos 1 and 2, below. Further details of the test are given in Annex VII.

### 7.2 Flexibility test

Compliance shall be with an AQL of 4.0.

When a 20 g weight is applied to one of the horizontal arms of the T frame for a period of 20 seconds at a distance 12 mm from the vertical arm, the deflection of the horizontal arm measured at the end of the arm shall be as follows:

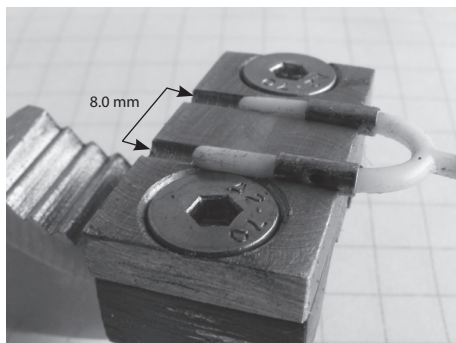


Photo 1. Arm Geometry

For freshly manufactured T frames that are greater than 24 hours but less than 96 hours from time of moulding: within the range 4.8 mm to 6.5 mm.

For T frames that are older than 96 hours: greater than 4.0 mm.

The test shall be carried out at a temperature of  $(23 \pm 2)$  °C. Before testing, the T frames shall be stored for at least 6 hours at the test temperature.

A suitable test rig 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 rig is shown in Photo 3, next page. If such a test rig is used, the T frame arm deflection may be converted into a scale reading using the appropriate amplification factor for the rig.

### 7.3 Copper collar retention force

Compliance shall be with an AQL of 4.0.

The minimum force required to displace a collar on the arm shall be 6.86 Newton (700 g-force) when tested using a separation speed of  $(200 \pm 20)$  mm/min.

During the copper collar retention force test, the T frame 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.

Optionally, one collar may be clamped in one jaw and the other collar clamped in the opposing jaw. The clamp(s) gripping the copper collar shall have a groove

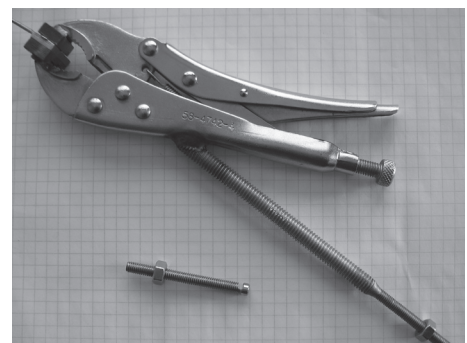


Photo 2. Grip overview

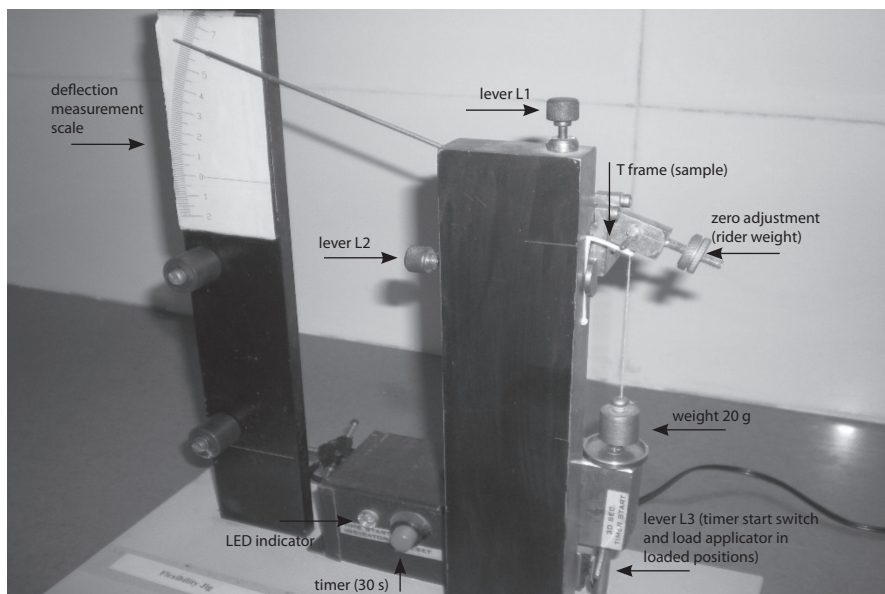


Photo 3. Flexibility apparatus (source: Corporate Channels, Ltd.)

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.

#### 7.4 Memory

Sampling shall be 20 units per LOT irrespective of LOT size.

When the finished product after sterilization is tested according to relevant clause of *ISO 7439*, the maximum displacement from horizontal of the horizontal arms shall be not greater than 5.0 mm.

#### 7.5 Thread knot

The knot shall be secure and not promote breakage under normal use.

Compliance shall be with an AQL of 0.65.

#### 7.6 Insertion instrument

The insertion rod shall be a snug fit but slide smoothly within the insertion tube and shall not trap the thread.

#### 7.7 Flange displacement force

Compliance shall be with an AQL of 0.65.

The required force to achieve a steady displacement of the flange should be between 2.0 and 9.0 Newton.

### 8 Packaging

Packaging shall comply with *ISO 11607* Part 1.

Sampling shall be in accordance with *ISO 2859-1*, Inspection Level S-4 unless otherwise stated.

Compliance shall be with an AQL of 0.65 unless otherwise stated.

Continuous polymer films shall be used to reduce the risk of tarnishing, unless ethylene oxide is used for sterilization, in which case a suitable ethylene oxide permeable film meeting the requirements for microbiological barrier properties specified in *ISO 11607-1* shall be used.

#### 8.1 Sealed pouch

TCu380A IUDs shall be packed in individual sealed pouches.

Sampling shall be 20 units per LOT irrespective of LOT size.



## 8.2 Sealed pouch integrity

Compliance shall be with an AQL of 0.65.

Sealed pouch integrity shall be tested according to *ASTM D 3078* (standard test method for determination of leaks in flexible packaging by bubble emission).

If permeable packaging material is used, sealed pouch integrity shall be tested by *ASTM F 1929:2004* (standard test method for detecting seal leaks in porous medical packaging by dye penetration).

## 8.3 Sealed pouch peel strength

When tested according to *ASTM F 88* (standard test method for seal strength of flexible barrier materials), the peel force shall be not less than 4.4 N/2.54 cm and not greater than 19 N/2.54 cm.

- If the packaging is made from two equally flexible materials, Technique B of *ASTM F 88* 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 F 88* shall be used (sample supported at an angle of 180°).

## 8.4 Labelling and inserts

Information required in accordance with *ISO 7439*, including information intended for the end user, shall be provided in accordance with the contractual requirements agreed with the purchaser. Up-to-date information on IUDs can be obtained from WHO publications already referenced in this document (see Section 1).

The following information shall be supplied:

The **Latest Insertion Date** (LID) is the date after which the product cannot be inserted *in utero*.

The **Latest Insertion Date** shall be printed on the sealed pouch and shall be based on the maximum product shelf-life from the date of sterilization.

The sterilization shall be completed within 30 days of sealing the finished device in the pouch.

In addition, 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.

Sampling shall be 20 units per LOT irrespective of LOT size.

## 8.5 Printing

All printing shall be clear and readily legible.

Sampling shall be 20 units per LOT irrespective of LOT size.

## 8.6 Cleanliness

The device, insertion tube, insertion rod, flange and any insert, such as instructions included in the package, shall be free of visible particulate matter.

Sampling shall be 20 units per LOT irrespective of LOT size.

# 9 Sterility

## 9.1 Sterilization method

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.

## 9.2 Sterility assurance level

The sterilization assurance level shall be  $10^{-6}$ .

## 9.3 Residual ethylene oxide levels

If ethylene oxide sterilization is used, then residual ethylene oxide levels shall not exceed 10 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.

### 10 Latest insertion date (LID)

The maximum permitted shelf-life for storage of the device prior to insertion is 5 years. This defines the **Latest Insertion Date (LID)**.

A 2-year transition period from the date of publication of this specification (December 2010) to implement this requirement has been agreed with the manufacturers.

Shelf-life claims shall be supported by appropriate real-time stability data. Accelerated ageing stability studies may be submitted pending the completion of real-time studies.

Guidance on conducting accelerated ageing stability studies is given in Annex V: Accelerated Ageing Testing.

When conducting stability studies, manufacturers shall include products assembled from components that have been stored for the maximum component storage periods specified in their documentation.

### 11 Materials procurement—Good Manufacturing Practice (GMP)

Manufacturers shall take appropriate steps to ensure that batches of compounded materials (T frame and thread materials) are not contaminated by any extraneous impurities during compounding operations.

Manufacturers shall document and control the procedures for the compounding of the T frame polymer.

Where lubricants are used in moulding, the grades shall be “Food Grade” and/or suitable for medical device manufacture.

Manufacturers shall introduce procedures to monitor and control the degree of tarnish and rough edges on the copper components.

If appropriate, the copper components should be cleaned prior to assembly.

### 12 Dimensional tolerances and manufacturing tolerance specifications

The nominal specified dimensions and tolerances may not provide the correct clearance for components such as the insertion rod, which must slide smoothly, and the flange, which has to have the correct displacement force.

It remains the responsibility of the manufacturer to produce a fully functioning, safe and effective product within the dimensional tolerance limits provided.

### 13 Workmanship

Finished IUDs should be inspected visually for evidence of visible defects and poor workmanship. Defects are divided into two categories, depending upon the level of impact they may have on the safety, effectiveness and acceptability of the product.

Defects that might affect the safety and/or effectiveness of the product are classified as critical defects and an AQL of 0.65 is applied.

Defects that might affect the acceptability of the product, causing the device to be rejected at the time of insertion, but that are not expected to affect safety or effectiveness are classified as non-critical defects, and an AQL of 2.5 applies.

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.

#### Critical defects:

Sampling shall be in accordance with *ISO 2859-1*, Inspection Level S-4.

Compliance shall be with an AQL of 0.65.

Assessed by visual examination, not measurement:

- a) severe tarnishing
- b) missing components
- c) flash on the mould lines of the T frame
- d) sharp protruding edges and burrs
- e) unsecured thread (including loose knot)
- f) incomplete/deformed ball
- g) deformed collars
- h) improperly sealed pouches
- i) empty pouches
- j) embedded and/or surface foreign particles.

#### **Non-critical defects:**

Sampling shall be in accordance with *ISO 2859-1*, Inspection Level S-4.

Compliance shall be with an AQL of 2.5.

Assessed by visual examination, not measurement:

- a) insertion rod bent or distorted
- b) discoloration of insertion tube or rod
- c) damaged packing cartons—depending on severity
- d) slight tarnishing.

For additional information refer to Section 1, Chapter 3.

## **14 Sampling**

The quality of a LOT is estimated by testing a randomly selected sample of IUDs from that LOT. The sample sizes are defined in the specification, using sampling plans specified in *ISO 2859-1 Sampling Procedures for Inspection by Attributes. Part 1. Specification for Sampling Plans Indexed by Acceptable Quality Level (AQL) for Lot-by-Lot Inspection*.

These are the most widely used sampling schemes for assessing attribute criteria (i.e. whether the product conforms or does not conform to the requirements detailed in the specification). Reference to the standard should be made to select the appropriate sample size and acceptance number based on the LOT size.

Where indicated, manufacturers and testing laboratories may opt to sample in accordance with *ISO 3951-1 Sampling Procedures for Inspection by Variables*.

### *Part 1. Sampling Schemes Indexed by Acceptance Quality Limit (AQL) for Lot-by-Lot Inspection.*

The same inspection levels and AQLs apply irrespective of whether sampling by attributes or by variables is used.

In cases of dispute, sampling according to *ISO 2859-1* shall be used.

Manufacturers may elect to use single, double or multiple sampling plans, depending upon the quality levels that they are achieving. The use of the switching rules to provide maximum consumer protection is strongly recommended. Refer to *ISO 2859-1* for more information.

Sample sizes and acceptance numbers for single sampling plans for normal inspection, indexed by LOT size, AQL and inspection level, are summarized in Tables 1 and 2, next page.

If the LOT size is not known or cannot be estimated, then a minimum sample equivalent to a LOT size of at least 1201–3200 should be used.

It should be noted that more reliable assessment of compliance with the specification is achieved with larger sample sizes. In testing a small LOT, consideration should be given to using a sample size specified for testing a bigger LOT (e.g. 10,001 to 35,000) if the test results are critical (for example, if a single LOT is being assessed).

Sampling for independent testing should be done by either an independent accredited laboratory or an independent sampling organization and not by the factory producing the IUDs. Such sampling is required for prequalification and pre-shipment compliance testing.

The sampler must verify the integrity of the LOT prior to sampling<sup>5</sup>.

<sup>5</sup> LOT integrity is the assurance that all items in the LOT are traceable to that LOT and were made in a single manufacturing run using the same batches or lots of raw materials.

<b>Table 1. Recommended sample sizes for Inspection Level S-4</b>								
LOT size	AQL 0.65		AQL 1.0		AQL 1.5		AQL 2.5	
	Size	Ac	Size	Ac	Size	Ac	Size	Ac
1,201 to 3,200	20	0	50	1	32	1	32	2
3,201 to 10,000	20	0	50	1	32	1	32	2
10,001 to 35,000	80	1	50	1	50	2	50	3
35,001 to 150,000	80	1	80	2	80	3	80	5

Ac = acceptance number

<b>Table 2. Recommended sample sizes for Inspection Level G-1</b>								
LOT size	AQL 0.65		AQL 1.0		AQL 1.5		AQL 2.5	
	Size	Ac	Size	Ac	Size	Ac	Size	Ac
1,201 to 3,200	80	1	50	1	50	2	50	3
3,201 to 10,000	80	1	80	2	80	3	80	5
10,001 to 35,000	125	2	125	3	125	5	125	7
35,001 to 150,000	200	3	200	5	200	7	200	10

Ac = acceptance number

Samples must be:

- taken in accordance with a pre-agreed sampling procedure<sup>6</sup>
- representative of the LOT of IUDs
- randomly selected (preferably based on random numbers)
- taken by, or under the personal full-time supervision of, the sampler.

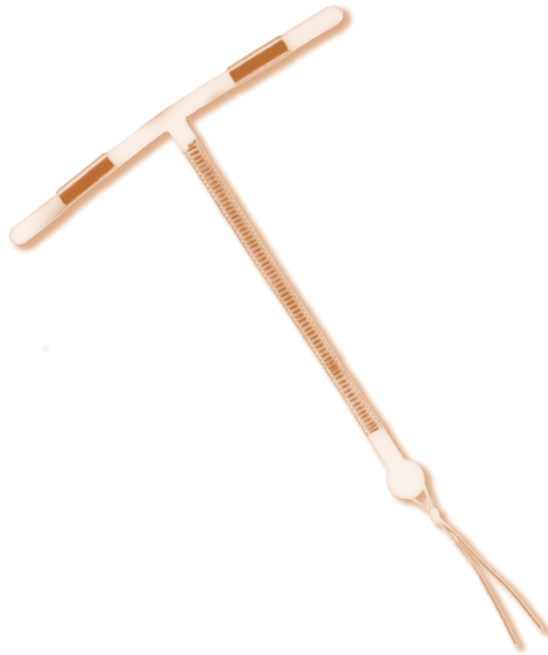
At the request of the manufacturer or buyer, a duplicate sample may be taken for use in case of disputes and can either be sent to the test laboratory or sealed with tamper-proof tape and left at the factory. The sampling agency must issue a report on the sampling process, detailing the sampling protocol, identification of the cases from which the individual samples were taken, and the total number of cases offered for sampling. For buyer reference at receipt, the sampler must mark the cases from which samples were taken.

The sample, once taken, must be sealed and dispatched to the test laboratory under the sampler's supervision.

<sup>6</sup> An example of an acceptable sampling procedure for determining the number of cases from which to draw the sample is the Square Root + 1 Plan. Under this procedure the number of cases from which to take samples is determined by calculating the square root of the total number of cases in the LOT (e.g. the square root of 100 = 10), plus one additional case. This number of cases is selected at random, for example, by using appropriate random numbers. The total number of samples required for testing specified by the sampling plan (*ISO 2859-1* or *ISO 3951-1*) is then selected equally from among the cases. Again, selection of the samples from each case shall be random.

## **SECTION ONE**

### **WHO/UNFPA TCU380A INTRAUTERINE DEVICE (IUD) SPECIFICATION, 2010**



## **CHAPTER 2**

### **Preparation of the Updated TCU380A Intrauterine Device (IUD) Specification, 2010**



## SECTION ONE

### CHAPTER 2: PREPARATION OF THE UPDATED TCU380A INTRAUTERINE DEVICE (IUD) SPECIFICATION, 2010

*The Technical Basis Paper, Annex 1, identified the issues that needed to be addressed to update the 1984 Population Council Specification. This chapter details the process used to address these issues and reach the conclusions and recommendations detailed in this manual.*

#### 1 Background

The original TCU380A IUD specification was developed by the Population Council and formed part of the New Drug Application submission (NDA 18–680) made to the U.S. Food and Drug Administration (USFDA). The product was cleared by the USFDA for marketing in 1984. The copy of the specification available for review by the IUD Technical Review Committee was undated but appeared, based on documents included in the specification, to have been prepared in the early 1980s.

IUD manufacturers made available for review by the committee a summary table of the principle requirements of the specification, focusing mainly on the dimensions originally developed by the manufacturers.

Since publication of the original specification over 25 years ago, there have been many changes in the basic principles of specification writing. In addition, a revised ISO standard for IUDs has been published, and standards relating to materials and test methods included in the specification have been updated.

There have also been significant changes in manufacturing practice for sterile medical devices, and radiation sterilization has become the method of choice for many types of products. It was recognized in the early phase of developing the prequalification scheme for the TCU380A IUD that, in light of all these changes, a new specification for the product was needed. Furthermore, research was required into the *in utero* ageing behaviours of the materials.

#### 2 Procedure

A Technical Basis Paper was prepared identifying issues to be addressed to update the original specification. Between 7 May and 6 August 2007, telephone and Internet consultations with IUD manufacturers were undertaken to confirm specification details, establish

current best practices, identify potential issues and address a series of questions raised during the preparation of the Technical Basis Paper. In addition, FHI conducted a series of tests on products from current manufacturers to assess compliance with the original specification and to help identify any issues regarding quality and testing.

WHO and UNFPA convened an IUD Technical Review Committee Meeting in August 2007 to discuss with technical advisers and experts from industry the issues raised in the Technical Basis Paper and the FHI test results. On the basis of these discussions, a revised specification was drafted, and a list of technical issues that needed further investigation was prepared. Both documents were circulated for review to the technical experts attending the meeting and the manufacturing community (<http://tiny.cc/tt5wr>).<sup>1</sup>

The draft specification and technical issues were then reviewed with the experts who had been invited to the August 2007 meeting. The draft specification was then amended at a meeting held on 26 October 2007 and following further consultations with committee members, industry experts and manufacturers, a revised draft of the specification was agreed at a meeting held on 19 March 2008 with WHO, UNFPA and key experts. The draft was again circulated for review and revised in September 2008. Between 2008 and 2010 research activities were implemented and electronic consultations were held to respond to unresolved issues.

A workshop was held in Bangkok, Thailand, on 12–15 January 2010, to which all TCU380A IUD manufacturers were invited. The revised specification, the research conducted in support of the changes to the specification and the WHO/UNFPA Prequalification Scheme for IUDs were presented and discussed in detail. The workshop afforded an opportunity for manufacturers to review and provide feedback to

<sup>1</sup> The hyperlink references shown as <http://tiny.cc/tt5wr> are to the manufacturers' community virtual network on the WHO Implementing Best Practice (IBP) Knowledge Gateway and are accessible only by the manufacturers and UNFPA and WHO staff. Requests for access to this site must be sent to UNFPA Procurement Section, Copenhagen, Denmark, <http://www.unfpa.org/public/procurement>.



the team that developed the revised specification. Following the workshop any unresolved issues raised by the manufacturers were dealt with through electronic communication and the specification was revised, extensively reviewed and finalized.

### 3 Specification changes

Documents generated during the review that summarize the major changes made to the specification and the rationale for these changes are archived (<http://tiny.cc/tt5wr>).

A summary of the major issues and the method in which they were addressed is given below:

1. The polymers used for construction of the frame, the thread and the application instrument were specified originally by brand or trade name and manufacturer. Some of these materials are no longer supplied for medical use, and some brand and trade names have changed. All polymers were therefore re-specified on a generic basis by polymer type and physical properties.

Typical properties of the specified (or equivalent) materials as reported by the material manufacturers were used to set the specifications. No changes were made to any existing specified performance requirements for the materials; these remain equivalent to those specified in the original Population Council specification. Radiation-resistant grades of ABS were introduced as an option for the insertion rod. Specification references, such as spectra, which are more properly the subject of a quality control plan and required for identity verification and which may be of use in ageing and oxidative damage studies, are intentionally excluded from the specification.

2. Improved specifications were developed for the fillers, namely barium sulphate and titanium dioxide. In the case of the latter, feedback from manufacturers indicated that the rutile polymorph should be specified. The upper limit of the barium sulphate has been retained at 24%, as given in the Population Council

specification, and not increased to 25%, as allowed by *ISO 7439*. Also, there is no evidence that allowing reduction of barium sulphate to 5% would give sufficient radio-opacity. As it is below the minimum 15% specified in *ISO 7439*, a 5% level could not be introduced without a specification design change and appropriate clinical consultation and trials.

3. An option to remove the requirement for a radio-opaque filler was reviewed with key medical opinion leaders. There was a strong reaction against its removal at this time. It was therefore agreed to retain the requirement to use barium sulphate as a filler.
4. The use of recycled material for the critical components, i.e. the frame and the suture, has been prohibited.
5. The copper wire was originally specified using a manufacturer's designation (Phelps Dodge). An equivalent grade has been specified using modern generic nomenclature.
6. The copper tube specification has been updated using modern generic grade designations. Copper collars must be deburred and polished to remove sharp edges.
7. There was discussion of adding limits for the degree of tarnishing of the copper components. Changes to packaging type and sterilization procedures have considerably reduced the risk of tarnishing. A definition of tarnishing has not been added because of the absence of an adequate, useable definition. It is the responsibility of the manufacturer to define and use appropriate scales in control of the product.
8. Frame dimensions have been converted into metric equivalents, and there has been some rationalization of the specified tolerances to bring them in line with current manufacturing practice. In most instances the original tolerances on dimensions were much tighter than the  $\pm 5\%$  permitted by *ISO 7439*. Where there would be no obvious consequences, the tolerances were relaxed, although in nearly all cases they still remain more stringent than permitted by



the ISO standard. The diameters of the copper collars can vary depending on the method of fixing; diameter requirements post-fixing have therefore been removed from the specification.

9. Performance and dimensional requirements were originally specified using a mix of different sampling procedures and plans, some of which were non-standard. Revised sampling procedures based on *ISO 2859-1* sampling plans (sampling by attributes) have been introduced. Sampling by variables was considered for some specification parameters in an attempt to reduce the sample sizes required for testing. However, when the proposed sampling plans were assessed using the FHI data, potential difficulties were identified, primarily because of the non-normal distribution of some of the measurements. Sampling by attributes was therefore retained for all performance parameters. Since the original assessment of the FHI data was conducted, there has been some relaxation of the tolerances in the specification. Sampling by variables according to *ISO 3951-1* may therefore be appropriate in some cases. Manufacturers and testing laboratories may elect to use sampling by variables to reduce sample sizes, but, when doing so, they should be aware of the limitations of this method as described in *ISO 3951-1*. In cases of dispute, sampling by attributes according to *ISO 2859-1* shall be used.
10. A test and requirement for frame flexibility was specified in the original Population Council specification. However, inadequate details were given about the equipment and test method. Also, questions were raised about the utility of the test because the copper collars can affect the outcome. Removing the collars prior to testing may affect the results. After careful consideration it was decided that the test is required since poor frame flexibility might affect the clinical acceptability of the device. Additional information on the test procedure including photographs of the equipment were obtained to allow the test to be adequately specified.
11. The original Population Council specification stated that the frame and thread materials shall meet US Pharmacopeia (USP) class II extraction limits for plastics. The testing requirements have been upgraded to those specified in *ISO 10993* for a mucosal membrane contacting medical device intended for permanent contact. As a consequence of updating to *ISO 10993*, it was agreed to delete USP testing, since testing to *ISO 10993* is more rigorous. Full testing according to *ISO 10993* is required for the initial qualification of new materials and if a significant change is made to the materials such as a change in grade or manufacturer.
12. The original Population Council specification required the screening of new LOTS (batches) of frame and thread materials using animal implant tests. Such routine animal testing would be unacceptable today. Alternative methods of screening for cytotoxicity using *in vitro* tests have been specified.
13. The proposal to specify the peak load at break for the thread has been adopted.
14. It was agreed to allow manufacturers to include, by agreement with the procurers, various devices that can assist insertion of the IUD. When considering design and choice of materials, manufacturers shall take into account the function of these devices, the type and duration of exposure to the body and the effect of sterilization by gamma radiation.
15. The preferred method of sterilization has been changed from ethylene oxide to radiation, in line with actual manufacturing practice. Ethylene oxide sterilization has been retained as an alternative.
16. A sterility assurance level of  $10^{-6}$  has been set, in line with current practice for sterile medical devices. A limit of one month between the date of packaging and the date of sterilization has been adopted.
17. The primary pack in which the device is sealed is now referred to in the specification as the “sealed pouch” to avoid any confusion between primary and secondary packaging.

18. The use of continuous plastic films for packaging has been added to the specification since such materials are compatible with radiation sterilization and provide improved levels of product protection, for example, against copper tarnishing. For this reason the use of continuous films is specified for radiation-sterilized products. (Continuous film materials cannot be used for ethylene oxide sterilization.)
19. Tests for pack integrity and pack seal strength using test methods as specified in appropriate ASTM standards have been introduced.
20. Finished product performance requirements have been rationalized and, where applicable, based on *ISO 7439* methods. Testing for device breaking strength (including the thread), copper collar retention force, frame memory and insertion instrument flange displacement force are now required.
21. During the revision of the specification, it was noted that the frame and thread materials are not formulated with antioxidants or other antidegradants. Given the long potential service life of the products, both in storage before insertion and *in vivo* after insertion, several of the experts expressed concern about this, especially considering that the preferred and normal method of sterilization is now by gamma irradiation. It was agreed, therefore, that follow-up work on the stability of the device is required.

A number of changes to the specification have been made as a consequence of this work, including adding the option for a radius at the junctions between the arms and the vertical stem. Research completed to date suggests that adding a radius might reduce the risk of fractures occurring at an arm-stem junction when the arms are bent upward, for example during flexing *in utero* or on removal.

Manufacturers adding a radius shall validate that the radius does not cause crush damage when the arms are bent down to load the device into the insertion tube.

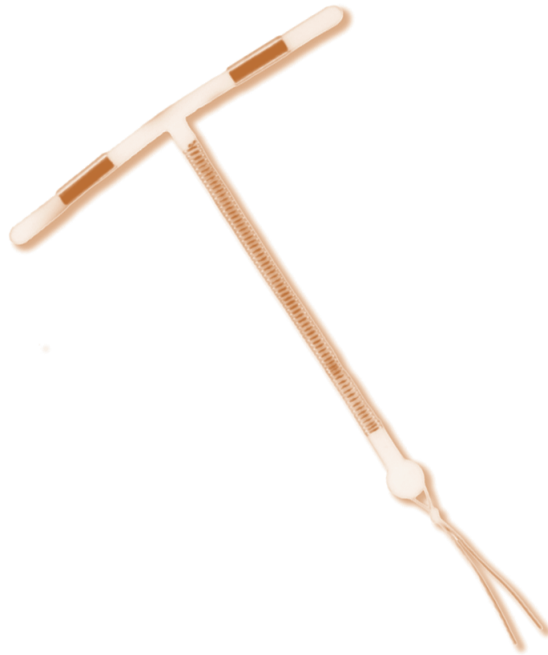
Further research on the impact of adding a radius to the arm-stem junction is strongly recommended.

#### **4. Research supporting the revision of the Population Council specification**

WHO/RHR funded a programme of research to investigate the physical and chemical properties of devices after removal from clients in a number of clinics in order to assess the degree, if any, of degradation occurring over the service life of the product. A summary of this work is given in Annex VI. The outcome of this research programme is now under review pending publication.

## **SECTION ONE**

### **WHO/UNFPA TCU380A INTRAUTERINE DEVICE (IUD) SPECIFICATION, 2010**



## **CHAPTER 3**

### **Workmanship and Visible Defects**



## SECTION ONE

### CHAPTER 3: WORKMANSHIP AND VISIBLE DEFECTS

#### 1 Introduction

All TCu380A IUDs in the sample will be inspected for workmanship. The number of IUDs exhibiting a visible defect will be recorded and classified either according to the types of defects listed below or as specified in the contract.

Visible defects will be classified as either (a) critical or (b) non-critical.

The IUD package will be inspected for visual defects with the IUD inserted.

#### 2 Types of defects

It is not possible to define all critical and non-critical defects, and it may be necessary to exercise some judgment about whether a particular visible defect is critical. If the visible defect may affect the performance of the IUD, the defect is considered critical.

If a defect that is not listed below or in the contract is considered critical by any party, then the purchaser, test laboratory and manufacturer must consult, discuss and agree on the classification of the defect concerned.

#### 2.1 Critical visible defects

Critical visible defects are those that either adversely affect the safety, effectiveness and performance of the IUD or are unacceptable to the consumer. Although there is no evidence that tarnishing affects the shelf-life or performance of the product, excessive tarnishing could cause the product to be rejected by the purchaser or end user.

IUDs having critical defects are, therefore, non-conforming. The most common critical defects are described in Table 3, and an AQL of 0.65 is recommended.

#### 2.2 Non-critical visible defects

Non-critical defects are defects that might affect the acceptability of the product, causing the device to be rejected at the time of insertion, but that are not expected to affect safety or effectiveness. They are considered minor defects, as they may not cause the IUD to fail the specification. Nevertheless, they are undesirable from the user's standpoint. If non-critical defects are specified in a purchase specification, then an AQL of 2.5 is recommended. The most common non-critical defects are listed in Table 4.

**Table 3. Critical visible defects**

<b>AQL 0.65</b>	
<b>Critical visible defect</b>	<b>Description</b>
Severe tarnishing of the copper	Severe discoloration of the copper sleeves and wire
Missing components	Missing sleeves or wire
Flash on the mould line of the T frame	
Sharp protruding edges and/or burrs	
Unsecured or missing thread	
Loose or incomplete knot	
Incomplete/deformed ball	
Deformed collars	
Improperly sealed pouches	
Empty pouches	
Embedded and/or surface foreign particles	

**Table 4. Non-critical visible defects**

<b>AQL 2.5</b>
<b>Non-critical visible defect</b>
Bent or severely distorted insertion rods
Some degree of tarnishing
Discoloration of plungers
Damaged packing cartons—depending on severity

3 Packaging defects

The primary packaging defects are listed in the specification (see Section 1, Chapter 1). Additional defects are sometimes detected only after shipment. This section summarizes common types of packaging defects, including those detailed in the specification.

3.1 Individual packages

The quality of the individual package shall be assessed by visual inspection, using a sampling plan in accordance with *ISO 2859-1*, Inspection Level S-3.

An AQL of 2.5 shall be applied to those defects collectively.

3.2 Consumer packs

There are no requirements for consumer packs included in the WHO/UNFPA Specification. Purchasers should fully specify requirements in

accordance with programme needs. Compliance should be assessed by visual inspection, using a sampling plan in accordance with *ISO 2859-1*, Inspection Level S-3.

It is recommended that an AQL of 2.5 be applied to consumer pack requirements.

The most common packaging visual defects are listed in Table 5.

3.3 Cartons and markings

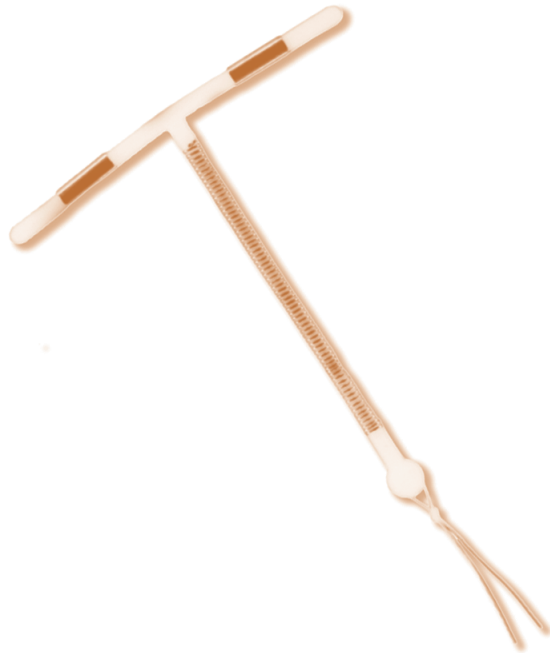
Purchasers should fully specify requirements in accordance with programme needs. Compliance should be assessed by visual inspection, using a sampling plan in accordance with *ISO 2859-1*, Inspection Level S-3.

It is recommended that an AQL of 4.0 be applied to carton requirements.

Table 5. Individual and consumer packaging defects
AQL 2.5
Packaging defect
Illegible or missing manufacture date, Latest Insertion Date, or LOT number
Damaged shipping cartons and inner packaging

## **SECTION ONE**

### **WHO/UNFPA TCU380A INTRAUTERINE DEVICE (IUD) SPECIFICATION, 2010**



## **CHAPTER 4**

### **Resolution of Disputes**





## SECTION ONE

### CHAPTER 4: RESOLUTION OF DISPUTES

#### 1 Introduction

There are a number of possible causes of disputes relating to quality during fulfilment of a contract to supply TCu380A IUDs. These may involve:

- interpretation of the contract
- payment schedules
- delays in delivery schedules
- completion schedules
- independent laboratory test results
- design issues
- condition of the IUDs upon arrival in-country or at some time after delivery.

It is essential that the procurement contract specify a process for the resolution of any disputes that might arise over contract or product quality issues.

#### 2 Disputes over laboratory results

Disputes over product acceptance most often arise when independent testing determines that the product is not in compliance with the required specification or standard. It is also possible for a manufacturer to dispute a decision made by the sampling agency regarding product packaging or appearance.

In most cases manufacturers accept the results of independent laboratories and replace LOTS that have been rejected. When they question the results, they usually present their own test results or other evidence to suggest that the independent tests are incorrect and do not accurately represent the quality of the product tested.

#### 3 Sources of disputes arising from laboratory testing

Laboratory testing is always done on a sample from the production LOT. There are generally two main sources of uncertainty in test results:

- **The uncertainty arising due to sampling errors.** There is always an intrinsic level of uncertainty in estimating the properties of any population based on testing of a sample. This uncertainty decreases as the sample size is increased. The sampling plans specified in the specification generally provide a 95% to 99% probability that a LOT that is just within specification will be accepted. (For sampling plans with acceptance numbers of zero, the probability of acceptance can be as low as 90%.) There is, therefore, a small risk that LOTS of acceptable quality occasionally will be rejected.
- **Testing or reporting mistakes due to operator error, equipment malfunction, drifts in calibration, transcription errors and other causes.** These types of mistakes are, in principle, preventable and should be minimized by application of the quality management system and procedures outlined in *ISO 17025*.

In addition, there is the normal uncertainty associated with measurement. *ISO 17025* requires that test and calibration laboratories determine and report the level of uncertainty associated with the test procedures used.

There are a number of important consequences that have to be considered because of the inherent limitations in the sampling plans. These are:

- In any shipment of IUDs there is always a risk that some LOTS will be rejected even though they are in compliance with the relevant AQLs. Manufacturers can minimize this risk by ensuring that the process averages are maintained well below the AQL. For example, by operating with process averages that are half of the relevant AQLs, manufacturers can cut the risk of rejecting LOTS that are actually in compliance to less than 1%.
- Manufacturers and purchasing agencies should plan on the assumption that some LOTS, possibly up to 5%, might be rejected. Estimates of volume requirements and pricing should take into account the impact of LOT rejections. Again, manufacturers can keep down the percentage of LOTS rejected by maintaining process averages well below the relevant AQLs.

LOTS with defect levels slightly above the AQL have a significant chance of being accepted.

As a general rule, when the level of LOT failures exceeds 5% over a large number of LOTS, i.e. 50 or more, then doubts can be raised about the quality of the manufacturer's production. Similarly, if the percentage of LOTS rejected exceeds 10% in the short term (e.g. between 5 and 50 LOTS), then again doubts can be raised about the quality of the products. Finally, if any two LOTS in a sequence of five LOTS are rejected, there is a significant risk that the process average may exceed the AQL.

#### 4 Decisions on re-testing

Re-testing should be undertaken only when:

1. There is considerable evidence that the laboratory has made a mistake.
2. There is considerable evidence that the test result is not representative of the population from which the LOT is taken.

Because of the operating characteristics of the sampling plans specified in *ISO 7349*, which are primarily intended for the routine testing of a continuing series of LOTS, there can be a significant probability that a rejected LOT will be accepted on re-test even if the LOT is not in compliance with the relevant AQLs. This means that in many cases re-testing will lead to conflicting results.

Therefore, re-testing should be undertaken only when there is strong evidence that an error has been made.

Before a re-test is considered, all available data should be reviewed and discussed with the independent laboratory. If a manufacturer disputes a test result, the following issues should be considered in deciding whether to allow a re-test:

- What is the margin by which the product has failed to comply?
- Is the manufacturer's history of production for the client a good one?

- What is the nature of the difference between the manufacturer's and the laboratory's test results?

If there is a dispute over a LOT or shipment of IUDs, then the laboratory should keep the non-conforming IUDs until the dispute is resolved.

When the LOT concerned is part of an ongoing order and there is historical or concurrent data on at least 10 LOTS, the process average can be estimated. If this process average is within the AQL, a re-test may be allowed.

In all cases the manufacturer should bear the cost of a re-test, unless it can be demonstrated that it is likely that the laboratory has made a mistake.

#### 5 Re-testing

Where re-testing is done, the second test should be designed to give additional confidence about the result. For example, re-testing may be done using the next higher inspection level defined in *ISO 2859* than the one used for the first sample (e.g. G-2 instead of G-1).

Where possible, the re-tested sample should be taken from the laboratory's retained sample. If this is insufficient, or if the sample is suspect, a new sample will need to be taken.

If a result is disputed, the laboratory and the manufacturer should be asked to verify basic issues, including:

##### Independent testing laboratory

- Verify that testing was performed as prescribed in the test method applicable to the order concerned.
- Verify that test equipment was in proper working order and in calibration at the time of testing.
- Check on staff performance by looking at the relevant tester's results on other products tested at about the same time.
- Verify the identity of the test samples and that the normal precautions were taken not to damage the samples prior to testing.

- Verify the uncertainty estimates being applied to the measurements.

If the laboratory has any doubts about any of these issues, it should re-test the products free of charge.

**Manufacturer**

- Review manufacturing and test documents for completeness and for anomalies that may indicate problems.
- Review all the items above that the independent testing laboratory is required to verify.



## **SECTION TWO**

### **THE WHO/UNFPA TCU380A INTRAUTERINE DEVICE (IUD) PREQUALIFICATION SCHEME AND OPERATIONAL GUIDANCE**



## **CHAPTER 5**

### **WHO/UNFPA Prequalification Scheme for TCu380A Intrauterine Devices (IUDs)**



## SECTION TWO

# CHAPTER 5: WHO/UNFPA PREQUALIFICATION SCHEME FOR TCU380A INTRAUTERINE DEVICES (IUDS)

## 1 Introduction

### 1.1 Background

The United Nations, through its procurement agencies, supplies medicines and other health products to countries throughout the world and, therefore, requires access to a choice of products of acceptable quality, safety and efficacy.

WHO, UNFPA and other key partners have developed an evidence-based list of Reproductive Health Essential Medicines (2007). The list was subsequently approved by the WHO Expert Committee on Selection and Use of Essential Medicines and incorporated into the WHO List of Essential Medicines. From this list and on the recommendations of members of the Reproductive Health Supplies Coalition, it was agreed that WHO would include a core group of reproductive health essential medicines in the WHO Prequalification Scheme for Essential Medicines, implementation of which began in 2006. As part of this activity, it was agreed that UNFPA would take responsibility for the prequalification of copper-bearing IUDs and male latex condoms, and that the UNFPA scheme would be harmonized with that of the WHO Prequalification Scheme for Essential Medicines.

As part of its responsibility for normative work, WHO, together with key partners, supported the preparation of a Cochrane Review (1) on copper-bearing intrauterine devices. This review provided an evidence base to support the revision of the International Standard for IUDs, *ISO 7439:2002*. An IUD Technical Review Committee, convened by WHO in September 2006, reviewed the evidence on the safety, efficacy and performance of copper-bearing IUDs and recommended the TCU380A intrauterine device (IUD) as the most appropriate device for bulk procurement by UNFPA. In addition, a detailed technical review process was undertaken between 2007 and 2009 to update the bulk procurement specification for TCU380A IUDs as detailed in Section 1, Chapter 2 and Annex 1: Technical Basis Paper.

This document describes the implementation of the Prequalification Scheme for the TCU380A IUD. It is supported by a specific UNFPA management system with detailed standard operating procedures (SOPs).

### 1.2 Objectives

The overall objective is to implement a scheme to prequalify manufacturers of TCU380A IUDs of assured quality at specific manufacturing sites for procurement by United Nations agencies. Specific objectives are to:

- promote the procurement of TCU380A IUDs from manufacturing sites that have been assessed as having the capacity to produce quality products;
- establish a system that promotes the procurement of quality products that retain their effectiveness throughout the stated shelf-life by conforming to the international standard *ISO 7439* and the *WHO/UNFPA TCU380A IUD Specification*;
- broaden and improve the quality of the supplier base for TCU380A IUDs that are deemed acceptable, in principle, for procurement by United Nations agencies;
- maintain and publish a list of prequalified suppliers.

## 2 The Prequalification Scheme for TCU380A IUDs

### 2.1 Eligibility to participate

The Prequalification Scheme is intended for manufacturers of TCU380A IUDs that undertake the processes of moulding, assembly, sterilization and packaging, as specified by UNFPA in the call for an Expression of Interest (EOI), referred to below.

The Prequalification Scheme does not apply to suppliers/agents engaged only with testing or re-packaging.

One or more of these processes may be carried out on a contract basis, but the manufacturer retains overall responsibility for product quality. An agent may respond to the Expression of Interest on behalf of a manufacturer who undertakes the process described above.



## 2.2 Expression of Interest (EOI)

### 2.2.1 Calls for and submission of Expressions of Interest (EOI)

Invitations to interested parties to submit an Expression of Interest (EOI) are published at regular intervals on the web sites of the UN Global Marketplace (UNGM): <http://www.ungm.org>; UNFPA: <http://www.unfpa.org/public/procurement>; WHO: <http://www.who.int/rhem/prequalification/9789241500999/en/index.html>; and RHR: [http://www.who.int/reproductivehealth/publications/family\\_planning/9789241500999](http://www.who.int/reproductivehealth/publications/family_planning/9789241500999).

The invitation is open and transparent. It invites manufacturers and/or their agents, described in 2.1 above, to submit an EOI for the products listed in the invitation. The applicants/manufacturers should submit their EOIs to the UNFPA focal point with the relevant information requested in the invitation. The applicants/manufacturers will be given a specified period to submit their responses from the time of publication of the advertisement. The information must be submitted in English (see this chapter, Clause 2.11 Language).

UNFPA will receive and record the EOI from each applicant/manufacture and issue an acknowledgement of receipt.

WHO and UNFPA provide further guidance on the submission of documentation for prequalification (see Section 2, Chapter 6; guidance is available on the web sites of UNFPA: <http://www.unfpa.org/public/procurement>; WHO: <http://www.who.int/rhem/prequalification/9789241500999/en/index.html>; and RHR: [http://www.who.int/reproductivehealth/publications/family\\_planning/9789241500999](http://www.who.int/reproductivehealth/publications/family_planning/9789241500999)).

When submitting an EOI for product evaluation, the applicant/manufacture should send to the UNFPA focal point the following:

- a covering letter expressing interest in participating in the UNFPA prequalification procedure and confirming that the information submitted in the Product Dossier and Site Master File summary is complete and correct;
- a Product Dossier in the format specified in the WHO/UNFPA guidance documents for submitting product data and information;

- product samples, as examples of products produced;
- a Site Master File summary for each manufacturing site listed in the Product Dossier, in the format specified in the WHO/UNFPA guidance documents for submitting a Site Master File summary; refer to Chapter 6, Clause 3 of this document.

The information must be accompanied by copies of all current certifications/accreditations; all manufacturing licences/registrations held; a copy of the company registration; copies of certificates and relevant documentation as applicable to the country of manufacture; documentation of the principal place of incorporation (for applicants that are corporations); specific certification/licences required in the country for manufacturing and exporting; and other legal documents such as trading certificates. Contact information of bankers, including all appropriate banking account references and codes, shall be included.

The documentation should be submitted in English by courier or registered mail (see this chapter, Clause 2.11 Language). A manufacturer/applicant may also provide a CD-ROM of this material. A CD-ROM must be in addition to, and not in place of, the printed copy of the documentation.

### 2.2.2 Assessment of documents submitted

The aim of the assessment of submitted documentation will be to determine whether the applicant/manufacture meets the minimum requirements detailed in the relevant ISO standards<sup>1</sup> and the *WHO/UNFPA TCu380A IUD Specification*, detailed in Section 1, Chapter 1 of this document,<sup>2</sup> in respect of product quality and safety, production and quality management, regulatory approvals and capacity of production.

<sup>1</sup> ISO documents are available from: International Organization for Standardization, ISO Secretariat, 1, Chemin ch. de la Voie-Creuse, CP 56, 1211 Geneva 20, Switzerland (<http://www.iso.org>).

<sup>2</sup> The *TCu380A IUD: Specification; Prequalification and Guidelines for Procurement, 2010* is also available on the web sites of UNFPA: <http://www.unfpa.org/public/procurement>; WHO: <http://www.who.int/rhem/prequalification/9789241500999/en/index.html>; and RHR: [http://www.who.int/reproductivehealth/publications/family\\_planning/9789241500999](http://www.who.int/reproductivehealth/publications/family_planning/9789241500999).

#### 2.2.2.1 Initial screening of documentation

UNFPA will aim to screen the submitted documentation within 30 days of the closing date for responses, to ascertain whether it contains all the required information.

If the submission is incomplete, the applicant/manufacturer will be informed and requested to complete the dossier within a specified time period. If the document remains incomplete, it may be rejected.

Dossiers that are considered complete as the result of the administrative screening will be retained by UNFPA for evaluation.

UNFPA will exchange letters with the applicant/manufacturer covering provisions of confidentiality and the process of assessment of submitted information and the scheduling of possible site inspection.

#### 2.2.2.2 Assessment of the Product Dossier and the Site Master File summary

UNFPA aims to convene a group of experts acting as assessors to complete the assessment of the Product Dossier and the Site Master File summary within a specified time period (90 days) of the closing date for receipt of responses.

The submissions will be evaluated by assessors having documented qualifications and relevant experience. The selection of assessors and the assessment will be done in accordance with existing United Nations procedures for the selection of consultants and experts. The team of assessors may include one or more inspectors responsible for subsequent inspections of the manufacturing sites. The assessors must comply with the confidentiality and conflict of interest rules of UNFPA, as laid down in Clauses 3 and 4 of this chapter.

The assessment of the submitted documentation will be done in accordance with standard operating procedures (SOPs) established by WHO/UNFPA for that purpose. To ensure uniformity in evaluation and timeliness of assessment activities, UNFPA will, if needed, provide training to the assessors.

In making its assessment, UNFPA may take into account information submitted by the applicant during previous applications that may be in UNFPA's

possession, including results from previous site inspections and laboratory test results on products produced by the manufacturer.

UNFPA aims to advise the applicant/manufacturer of the outcome of the assessment of documentation within 30 days after its completion. If applications are found to be in compliance with the UNFPA requirements, as detailed in this document and on the WHO and UNFPA web sites, inspection of the manufacturing site will be scheduled.

### 2.3 Site inspection

UNFPA will plan and coordinate inspections at the relevant manufacturing sites to assess the manufacturing process and the product and quality management systems for compliance with general and performance requirements of the *WHO/UNFPA TCu380A IUD Specification* and good management practice as specified in, but not limited to, the following international standards<sup>3</sup>:

- *ISO 7439. Copper-Bearing Intra-uterine Contraceptive Devices—Requirements, Tests*
- *ISO 13485. Medical Devices—Quality Management Systems: Requirements for Regulatory Purposes*
- *ISO 10993. Biological Evaluation of Medical Devices*
- *ISO 11135–1. Sterilization of Health Care Products—Ethylene Oxide. Part 1. Requirements for Development, Validation, and Routine Control of a Sterilization Process for Medical Devices*
- *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. Guidance on Dosimetric Aspects*
- *ISO 11607. Packaging for Terminally Sterilized Medical Devices.*

<sup>3</sup> Please note that reference to the date of publication has not been stated. The latest available published version of the standard should be used.

### **2.3.1 Inspection team**

The inspection will be performed by a team consisting of one or more experts appointed by UNFPA, who will act as temporary advisers to UNFPA. The inspectors must have documented qualifications, detailed knowledge of the process for manufacturing IUDs, experience in auditing and quality management systems and specific experience inspecting IUD manufacturing sites. The inspectors must comply with the confidentiality and conflict of interest rules of UNFPA, as detailed in Clauses 3 and 4 of this chapter. To ensure uniformity in inspection procedures, UNFPA has prepared an SOP and, if necessary, can provide training to these experts.

Where possible, UNFPA will appoint at least one inspector able to communicate and read the local language. Failing this, an interpreter selected by UNFPA will be used. One member of the team will be designated by UNFPA as the “lead inspector” and will be responsible for the coordination of inspection activities and production of the report. The team may include observers from UNFPA. UNFPA will advise and seek the involvement of the national competent body in the on-site inspection.

UNFPA will advise the manufacturer in advance of the composition of the team performing the site inspection and the identity of each inspector and will provide their curricula vitae. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to UNFPA prior to the visit. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member’s participation in the site visit. Such an objection must be made known to UNFPA by the manufacturer within 10 days of receipt of information on the composition of the proposed team. In the event of such an objection, UNFPA may cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

So as to ensure a standardized approach, each team will perform the inspections and report on its findings to UNFPA in accordance with the SOPs established by UNFPA for that purpose.

Information submitted in response to the EOI and the assessment report will be made available to the inspectors. All inspectors must comply with the confidentiality and conflict of interest rules of UNFPA as detailed in Clauses 3 and 4 of this chapter.

### **2.3.2 Scope and scheduling**

Prior to the inspection the applicant/manufacturer will be informed of the scope of the inspectors’ planned activities. The key components of the inspection are described in Section 2, Chapter 6 of this document and on the WHO/UNFPA web sites under the heading “Scope of manufacturing site inspection: TCu380A IUDs”. The inspection will not be limited to these components. Manufacturers must be prepared to show the inspectors all aspects of the manufacturing process, including sites for compounding, injection moulding, and sterilization and records and data that relate to the production of the IUDs. Where necessary, manufacturers must organize access to facilities of contractors who undertake off-site activities such as sterilization. Inspectors may, in consultation with UNFPA, schedule the review of such facilities into their site inspection.

UNFPA aims to advise the applicant/manufacturer of the date of inspection at least 30 days in advance. UNFPA and the inspectors will make efforts to accommodate reasonable requests made by the manufacturer and national regulatory authorities to change the dates of the inspection.

UNFPA will inform the applicant/manufacturer that the inspectors may request copies of documents presented as evidence during inspection and may request permission to make a photographic record of the inspection, subject always to consideration of confidential information, as referred to in Clauses 2.5, 3 and 4 of this chapter.

### **2.3.3 Transparency**

The inspection team is paid by UNFPA to inspect the facilities, and the members are reimbursed for their hotel and transport expenses by UNFPA. The manufacturer will not pay for hotel accommodation or make any payments for or to the inspectors and/or UNFPA staff. The manufacturers may be requested to assist in making reservations at an appropriate hotel and for local

transportation to and from the airport or station, and to and from the inspectors' hotel to the facilities.

The inspectors (and UNFPA staff who accompany the inspectors) cannot accept any gifts from the companies they visit. UNFPA requires that applicants/manufacturers do not make any offers of gifts of whatever value to the inspectors and/or UNFPA staff.

By participating in the scheme, the manufacturer agrees to allow full access to:

- any of the facilities that are in any way involved in the production of the product(s) concerned;
- all documentation related to that production.

If such access is not provided, the manufacturing site and specific products cannot be prequalified.

Any evidence of fraud or serious omissions by the manufacturer in the initial assessment procedure will lead to termination of the site inspection.

## 2.4 Product testing

Products will be sampled for independent testing prior or subsequent to the inspection by an independent sampler appointed by UNFPA or by the inspectors at an appropriate point during the site inspection.

The sample sizes are specified in *ISO 2859-1 Sampling Procedures for Inspection by Attributes*. These are the most widely used sampling schemes for assessing attribute criteria (i.e. whether the product conforms or does not conform to the requirements detailed in the specification).

The sampler must verify LOT integrity during sampling.

Samples must be:

- taken in accordance with a pre-agreed sampling plan
- representative of the LOT of IUDs
- randomly selected (preferably based on random numbers)
- taken by or under the personal full-time supervision of the sampler.

The sample, once taken, must be sealed and dispatched under the sampler's supervision. The inspector(s) may either take the samples with them or else arrange for the manufacturer to have the sealed boxes sent to the selected laboratory by courier at UNFPA's expense. A report summarizing the process should be submitted and should include identification of the cases from which the samples were taken and the number of cases offered for sampling.

The range of tests performed will be in accordance with the current *WHO/UNFPA TCu380A IUD Specification*. All product testing will be undertaken by independent accredited test laboratories selected by UNFPA. Such test laboratories must possess defined and documented competence and experience, as demonstrated by accreditation to the current *ISO 17025* standard.

A copy of the test report will be provided to the manufacturer.

## 2.5 Report and communication of the results of the site inspection

At the conclusion of the inspection, the inspectors will prepare a brief written summary report outlining the key findings and observations discussed with the manufacturer during the site inspection. This report will be provided to UNFPA with a copy to the manufacturer.

In addition, the inspection team will complete its full report according to the established UNFPA SOP and format, describing the findings, evidence and recommendations. The report will be submitted to UNFPA.

The inspection report will be communicated by UNFPA to the applicant and/or manufacturer. If any additional information is required, or corrective action has to be taken by the manufacturer(s), UNFPA will postpone its decision on the acceptability of the site(s) involved until such information has been evaluated or the corrective action has been taken and found satisfactory in accordance with the time frame and recommendations made by the UNFPA inspectors.



UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the applicant/manufacture is not able to either provide the required information or implement the corrective actions in a specified time period, or if the information supplied is inadequate to complete the quality assessment process.

In the event of any disagreement between an applicant and UNFPA, an SOP established by UNFPA for the handling of appeals and complaints will be followed to discuss and resolve the issue.

The ownership of any of the reports produced in the course of, or as the result of the assessment of documentation, product testing and inspection of the manufacturing site lies with UNFPA. Thus, UNFPA shall be entitled to use and publish such reports and/or a summary of a report, subject always, however, to the protection of any commercially confidential information of the applicant/manufacture(s).

Confidential information may include:

- confidential intellectual property, “know-how” and trade secrets (including, e.g. formulas, programmes, processes or information contained or embodied in a product, unpublished aspects of trademarks, patents);
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the exchange of letters, to be concluded before the assessment of the Product Dossier or inspection of the manufacturing site(s), between UNFPA and each applicant/manufacture.

Notwithstanding the foregoing, UNFPA and WHO reserve the right to share a summary and/or the full evaluation and inspection reports with the relevant authorities of any interested Member State of UNFPA and/or WHO.

## 2.6 Decision to prequalify

It is UNFPA’s responsibility to compile the information submitted in response to the EOI, the assessment report, the inspection report and the test report. A UNFPA staff member with

appropriate experience and training will assess the information about each applicant/manufacture and, in consultation with the assessors and inspectors, will make a final decision about the outcome of the prequalification process.

Based on this assessment UNFPA will either:

- Prequalify the TCu380A IUD manufacture at a specific site without conditions. This will only be the case when there is no evidence that corrective action is required.

or

- Require the manufacture(s), where deemed necessary, to undertake specified corrective action(s). The inspectors may also recommend further inspection and/or product testing once the corrective actions have been completed. The manufacture must carry out the corrective action within an agreed time period and provide UNFPA with evidence, where required, showing that the corrective action has been taken. If UNFPA is satisfied with this additional information, the manufacturing site will be added to the list of prequalified TCu380A IUD manufacturing sites.

or

- Determine that a manufacturing site is ineligible for prequalification (without any requirement for corrective action being offered). This will not, however, preclude the applicant/manufacture from resubmitting an application in response to future invitations for EOIs.

Where the inspectors recommend corrective action requiring a subsequent inspection, the manufacture must advise UNFPA within an agreed period of time that corrective action has been completed and provide the relevant evidence, if required. The recommendation for corrective action may include further independent product testing. After review of the evidence, UNFPA will decide whether or not to schedule a further inspection.

If a further inspection is deemed necessary, the inspection process and assessment will be implemented in accordance with the procedure detailed in Clauses

2.3, 2.4, 2.5 and 2.6 of this chapter. Any re-inspection will be at the expense of the manufacturer.

UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the applicant/manufacture is:

- not able to provide the required information; and/or
- unable to implement the corrective actions in a specified time period; and/or
- if the information supplied is inadequate to complete the quality assessment process.

The findings of the inspection may include non-mandatory observations aimed at highlighting potential for improved manufacturing and quality management practices.

If evidence supporting mandatory improvement actions or additional information is required, or other corrective actions have to be taken by the manufacturer, UNFPA will postpone its final decision until: (a) such information has been evaluated or (b) the corrective action has been taken and found satisfactory in light of the specified international standards, as detailed in the references of this chapter or as deemed appropriate by the inspector.

If the applicant/manufacture has not submitted a satisfactory response within 12 months of submission of the report to UNFPA, the application will lapse and the applicant/manufacture will need to re-apply in response to a future invitation for EOI.

Each applicant/manufacture will receive a letter from UNFPA informing the applicant/manufacture of the outcome of the quality assessment process. UNFPA aims to inform the applicant/manufacture of the results of the process within 30 days of receipt of all final reports.

## **2.7 Listing of prequalified TCu380A IUDs and manufacturing sites**

Once UNFPA is satisfied that the quality assessment process is complete, and where the Product Dossier, Site Master File summary and

corresponding manufacturing site have been found to meet the prequalification requirements, the product as produced at the specified manufacturing site(s) will be listed on the prequalification web sites for UNFPA: <http://www.unfpa.org/public/procurement>; WHO: <http://www.who.int/rhem/prequalification/9789241500999/en/index.html>; and RHR: [http://www.who.int/reproductivehealth/publications/family\\_planning/9789241500999](http://www.who.int/reproductivehealth/publications/family_planning/9789241500999).

The list of prequalified TCu380A IUDs and corresponding manufacturing sites will be compiled and updated in accordance with an SOP established by UNFPA for this purpose.

## **2.8 Maintenance of the prequalified status**

Once the product is included in the list of prequalified TCu380A IUDs and corresponding manufacturing sites, the applicant/manufacture shall be required to inform UNFPA, within four weeks, of any matter that affects the information on which approval was based. This includes prior notification of any intended changes in the manufacturing site and manufacturing process. It may also include, but is not limited to:

- change of premises
- change in production and testing equipment
- change in senior management
- product recalls
- change in certifications or licences held by the manufacturer
- reports of adverse events
- change in design
- change in suppliers of raw materials
- change in specification of raw materials
- change in raw material processing
- change in production
- change in packaging
- change in sterilization processes
- new information about shelf-life.

It is the applicant's responsibility to provide UNFPA with the appropriate documentation, including appropriate test and validation protocols and other relevant documents, all referring to relevant parts of the Product Dossier and Site Master File summary, to prove that the implementation of any intended variation will not have an adverse impact on the quality of the product that has been prequalified. UNFPA will undertake an evaluation of variations according to established UNFPA guidelines and SOPs and communicate the outcome to the applicant/manufacture. Compliance with the requirement to report changes will be checked during the inspections carried out by UNFPA.

## **2.9 Periodic monitoring of the quality of the products produced by prequalified manufacturing sites**

At periodic intervals UNFPA may, through an independent sampler, take random samples of TCu380A IUDs produced by listed manufacturers. The sample size taken and range of tests performed will be in accordance with the current TCu380A specification.

All product testing will be undertaken by independent test laboratories, selected by UNFPA, of defined and documented accreditation to the current *ISO 17025* international standard. In the event of failure of the product to meet the established requirements for testing, UNFPA will investigate the problem and communicate this to the manufacturer and/or applicant, if different from the manufacturer.

UNFPA may request reports from consumer or regulatory bodies, or from other procurement agencies, relating to the quality and supply of the prequalified TCu380A IUD.

Complaints concerning prequalified TCu380A IUDs communicated to UNFPA will be investigated in accordance with an SOP established by UNFPA for that purpose. After investigation UNFPA will provide a written report of the complaint investigations, including recommendations for action, to the applicant/manufacture. UNFPA will require evidence of effective action taken, where relevant.

UNFPA will make the report available to the appropriate authorities of the country where the manufacturing site is located, subject always to

consideration of commercially confidential information, as referred to in Clause 2.5 of this chapter. UNFPA reserves the right to make such reports public, if it considers this to be of public health importance. In addition, UNFPA reserves the right to share the full report and/or recommendations for action with WHO and relevant authorities of interested Member States of the World Health Organization.

At periodic intervals UNFPA may request a summary of the statistical analysis of TCu380A IUD production from the manufacturer for demonstration of continued capability to manufacture to the *WHO/UNFPA TCu380A IUD Specification*. This may be accompanied by a request for selected evidence from management review, risk management, production, measurement and analysis and other records. Independent sampling organizations in the country may be asked to conduct the sampling of records and verify the links to the analysis results to which they have been related.

## **2.10 Reassessment of prequalified manufacturing sites**

UNFPA aims to undertake a reassessment of TCu380A IUDs manufactured at a specific site at intervals of no more than three years. Such reassessments will consist of a comprehensive evaluation of documentation, site inspection and product testing similar to the initial prequalification assessment.

Reassessment may also be required in the following situations:

- if the TCu380A IUD supplied by the manufacturer is considered by UNFPA or one or more of the other United Nations agencies not to be in compliance with the agreed TCu380A IUD specification;
- if a complaint considered serious in nature has been received by UNFPA or one or more of the other United Nations agencies or organizations;
- if there is a significant change in one or more of the items listed in Clause 2.8, above.

All relevant information including the reassessment of submitted documentation and the site inspection report, together with monitoring information, will be

considered by the designated UNFPA official, and a decision will be made to:

- maintain the TCu380A IUD and its manufacturing site on the list of prequalified products without need for corrective actions;
- or
- maintain the prequalification status of the TCu380A IUD and manufacturing site with a requirement for corrective actions and, where agreed to by UNFPA, further product testing and/or site inspection;
- or
- suspend prequalified status.

UNFPA aims to advise the applicant/manufacture of the result of the reassessment and make any necessary amendments to the list of prequalified manufacturing sites and products within 30 days of receipt of the data on which the decision is made. The updated list will be published on the WHO and UNFPA prequalification web sites.

UNFPA will de-list any prequalified product and manufacturing site if submitted information is subsequently found to be incorrect or fraudulent.

## 2.11 Language

The official language of the programme is English. All documents submitted as part of an application for prequalification will be in English. If the original of any required document is not in English, the manufacturer must submit a copy of the original, plus a certified translation into English. All correspondence between UNFPA and the applicant shall be in English. All reports issued by the assessors and inspectors and by UNFPA on the assessment and inspection will be in English.

Inspections will be conducted in English, where necessary with the aid of an interpreter. It is the responsibility of the manufacturer to advise UNFPA and for UNFPA to agree whether an interpreter is required for the inspection.

## 2.12 Fees

At present, except when the manufacturing site has to be re-inspected, UNFPA will cover the expenses

of the assessments, inspections and product testing. Manufacturers are responsible for their own costs related to providing the necessary information and help required under the Prequalification Scheme.

Currently, the process is conducted by UNFPA free of charge. UNFPA reserves the right, however, to charge a fee on a cost-reimbursement basis.

## 2.13 Resolution of disputes

If there is any disagreement between a manufacturer and UNFPA, an SOP established by UNFPA for the handling of appeals and complaints will be followed to discuss and resolve the issue.

## 3 Confidentiality undertaking

The assessors and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to UNFPA or parties collaborating with UNFPA in accordance with the terms set forth below.

Assessors and inspectors will take all reasonable measures to ensure:

- that confidential information is not used for any other purpose than the evaluation/inspection activities described in this document;
- that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of UNFPA (including by manufacturers);
- or
- was in the public domain at the time of disclosure by or on behalf of UNFPA (including by manufacturers);



or

- has become part of the public domain through no fault of theirs;

or

- has become available to them from a third party not in breach of any legal obligations of confidentiality.

#### 4 Conflict of interest

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest.

If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to UNFPA. In this connection each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete and that he/she will immediately notify UNFPA of any change in this information.

All inspectors furthermore agree that UNFPA will advise the manufacturer in advance of the identity of each inspector and composition of the team performing the site inspection and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to UNFPA prior to the visit. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member's participation in the site visit.

Such an objection must be made known to UNFPA by the manufacturer within 10 days of receipt of the confirmed date of the site inspection from UNFPA. In the event of such an objection, UNFPA reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

#### Reference

Kulier R et al. Copper containing, framed intra-uterine devices for contraception. *Cochrane Database of Systematic Reviews*, 2007 Issue 4, Art. No.: CD 005347. DOI 10.1002/14651858.CD005347.pub3.

#### Applicable standards

**Note:** Standards are undated; the latest edition should be referred to.

*ISO 7439. Copper-Bearing Intra-uterine Contraceptive Devices—Requirements, Tests.*

*ISO 13485. Medical Devices—Quality Management Systems: Requirements for Regulatory Purposes.*

*ISO/IEC 17025. General Requirements for the Competence of Testing and Calibration Laboratories.*

*ISO 10993. Biological Evaluation of Medical Devices.*

*ISO 11135–1. Sterilization of Health Care Products—Ethylene Oxide. Part 1. Requirements for Development, Validation, and Routine Control of a Sterilization Process for Medical Devices*

*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. Guidance on Dosimetric Aspects.*

*ISO 11607. Packaging for Terminally Sterilized Medical Devices.*

## **SECTION TWO**

### **THE WHO/UNFPA TCU380A INTRAUTERINE DEVICE (IUD) PREQUALIFICATION SCHEME AND OPERATIONAL GUIDANCE**



## **CHAPTER 6**

### **Operational Guidance—WHO/UNFPA TCu380A Intrauterine Device (IUD) Prequalification Scheme**



## SECTION TWO

### CHAPTER 6: OPERATIONAL GUIDANCE—WHO/UNFPA TCU380A INTRAUTERINE DEVICE (IUD) PREQUALIFICATION SCHEME

#### 1 Introduction

Products listed in the World Health Organization (WHO) Model List of Essential Medicines are those that satisfy the priority health care needs of a population. They are selected on the basis of, *inter alia*, disease prevalence, evidence of efficacy and safety, and comparative cost-effectiveness.

Products included in WHO treatment guidelines are selected on the basis of an assessment of the evidence of benefits, risks, costs and appropriateness for use in a variety of situations, taking into account the needs of special populations and the values and preferences of the groups (professional and patient) using them.

Prequalified manufacturing sites for TCU380A intrauterine devices (IUDs) offer products that, as part of the WHO/UNFPA Prequalification Scheme, have been found to be acceptable, in principle, for procurement by United Nations agencies.

The aim of the WHO/UNFPA Prequalification Scheme is to ensure that the applicant or manufacturer meets the minimum requirements set out in the relevant ISO standards<sup>1</sup> and *WHO/UNFPA TCU380A IUD Specification and Prequalification Scheme, 2010 (1)* in respect of product quality and safety, production and quality management, regulatory approval and production capacity.

The WHO/UNFPA Prequalification Scheme involves the following key activities:

- evaluation of documents submitted in response to an invitation for Expression of Interest (EOI);
- inspection of the manufacturing site;
- product testing;
- review of testing and inspection reports to make a decision about the acceptability of each applicant;
- publication and periodic updating of a list of prequalified products and manufacturing sites on the web sites of WHO: <http://www.who.int/rhem/prequalification/9789241500999/en/index.html>;

<sup>1</sup> ISO documents are available from: International Organization for Standardization, ISO Secretariat, 1, ch. de la Voie-Creuse, CP 56, 1211 Geneva 20, Switzerland (<http://www.iso.org>).

<http://www.who.int/rhem/prequalification/9789241500999/en/index.html>; UNFPA: [www.unfpa.org/public/procurement](http://www.unfpa.org/public/procurement); and RHR: [http://www.who.int/reproductivehealth/publications/family\\_planning/9789241500999](http://www.who.int/reproductivehealth/publications/family_planning/9789241500999).

Periodic reassessment of the prequalification status of the product and manufacturing sites will be undertaken at intervals of three years or less.

The WHO/UNFPA Prequalification Scheme has been harmonized with the WHO Prequalification Scheme for Essential Medicines and approved for publication by the 42nd WHO Expert Committee on Specifications for Pharmaceutical Preparations, October 2007, and published as WHO Technical Report, No. 948, May 2008 (2).

**The purpose of this guidance document is to outline the procedures required by WHO/UNFPA to:**

- respond to an invitation for Expression of Interest (EOI)
- prepare a Product Dossier
- prepare a Site Master File (SMF) summary
- support inspection of the manufacturing site.

#### 1.1 Invitation for Expression of Interest

Invitations to interested parties to submit an Expression of Interest (EOI) are published at regular intervals on the web sites of the United Nations Global Market Place: <http://www.ungm.org>; WHO: <http://www.who.int/rhem/prequalification/9789241500999/en/index.html>; UNFPA: <http://www.unfpa.org/public/procurement>; RHR: [http://www.who.int/reproductivehealth/publications/family\\_planning/9789241500999](http://www.who.int/reproductivehealth/publications/family_planning/9789241500999); and possibly through other media, such as the international press.

Each invitation will be open and transparent, inviting all relevant parties to submit EOIs for the products listed. The applicants/manufacturers will be given a specified period to submit their response from the time of publication of the advertisement.

In situations of high public health concern, as determined by WHO, UNFPA may also directly invite

relevant parties to submit their product for assessment by UNFPA under this procedure without publication of an invitation for EOIs.

Applicants/manufacturers should submit their EOIs in print to the UNFPA focal point with the relevant information requested in the invitation. The applicants/manufacturers may also provide a CD-ROM of this material. The CD-ROM must be in addition to, and not in place of, the hard copy of documentation. UNFPA will receive and record the EOI from each applicant/manufacturer and acknowledge receipt.

The official language of the Prequalification Scheme is English. All documents submitted as part of an application for prequalification should be submitted in English. If the original of any required document is not in English, the manufacturer must submit a copy

The Prequalification Scheme is intended for manufacturers of TCu380A IUDs that carry out moulding, assembly, sterilization and packaging, as specified by UNFPA in the invitation for an Expression of Interest (EOI). One or more of these processes may be carried out on a contract basis, but the manufacturer must retain overall responsibility for product quality. An agent may respond to the EOI on behalf of a manufacturer who undertakes the processes described above.

**The Prequalification Scheme does not apply to suppliers or agents engaged only in testing or re-packaging.**

of the original with a certified translation into English.

All correspondence between UNFPA and the applicant will be in English. All reports issued by the inspectors and by UNFPA on the inspections will be in English.

## 1.2 Data and information to be submitted

Interested applicants must submit to the UNFPA focal person the following documentation in hard copy:

- covering letter expressing interest in participating in the UNFPA prequalification scheme, confirming that the information submitted in the

Product Dossier and Site Master File summary is complete and correct;

- Product Dossier, in the format specified in the WHO/UNFPA guidance documents for submitting product data and information;
- product samples as examples of products produced;
- a Site Master File summary for each manufacturing site listed in the Product Dossier, in the format specified in the WHO/UNFPA guidance documents, as described in Clause 3 of this chapter;
- copies of all current certifications and accreditations, all manufacturing licences, registrations held, and a copy of the company registration;
- copies of certificates and relevant documentation as applicable in the country where the site is located, such as:
  - the principal place of incorporation (for applicants that are corporations);
  - specific certification/licences required in the country for:
    - manufacturing
    - exporting;
  - other legal documents, such as trading certificates;
  - contact information of bankers, including all appropriate banking account references and codes.

## 1.3 Process for submitting documentation

- Hard copies of all documents, in English, must be submitted with the letter of application.
- Documentation, in English, should be submitted by courier or registered mail.
- If possible, a CD-ROM with electronic copies of the documents should be included.
- The letter of application must clearly state: **“Request for prequalification for TCu380A IUDs”**.
- Applications for prequalification with supporting documents should be submitted in sealed envelopes no later than the date specified in the invitation for EOIs, clearly marked **“Application to prequalify for TCu380A IUDs”**.

The envelope must be addressed to:

**Response to Invitation for Expression of Interest**

**Invitation for Prequalification TCu380A IUD**

**Attention:** [insert name of UNFPA representative]

United Nations Population Fund (UNFPA)  
Headquarters

Procurement Section

Midtermolen 3, P.O. Box 2530

DK 2100, Copenhagen 0, Denmark

**Sector:** Reproductive Health Commodities Security

The back of the envelope should display the information shown in the box below.

Invitation for Expression of Interest

Managed by UNFPA Procurement Section,  
Copenhagen, Denmark

Application for prequalification

Country: UNFPA Headquarters, Copenhagen,  
Denmark

Sector: Reproductive Health Commodity Security

Development Business Print Edition, Issue  
Number: \_\_\_\_\_

Issue Date: \_\_\_\_\_

Expression of Interest Number: \_\_\_\_\_

Deadline: \_\_\_\_\_

UNFPA will receive and record the EOI from each applicant/manufacture and issue an acknowledgment of receipt.

UNFPA reserves the right to accept or reject late applications.

Further information regarding prequalification may be obtained from:

- a) the web sites of UNFPA (<http://www.unfpa.org/public/procurement>); WHO (<http://www.who.int/rhem/prequalification/9789241500999/en/index.html>); and RHR ([http://www.who.int/reproductivehealth/publications/family\\_planning/9789241500999](http://www.who.int/reproductivehealth/publications/family_planning/9789241500999)).

or

- b) by sending a request to the Officer in Charge, Prequalification, United Nations Population Fund, Midtermolen 3, P.O. Box 2530, DK 2100 Copenhagen 0, Denmark.

#### 1.4 Sample of the letter of application

##### PREQUALIFICATION OF TCu380A IUDs

Date .....

To: United Nations Population Fund  
Procurement Section  
Midtermolen 3, P.O. Box 2530  
DK 2100 Copenhagen 0  
Denmark

Sir/Madam:

Being duly authorized to represent and act on behalf of [name of manufacturer] (hereinafter referred to as the "Applicant") and having reviewed and fully understood all the information on prequalification provided, the undersigned hereby applies to be prequalified by UNFPA as potential suppliers of TCu380A intrauterine devices.

Attached to this letter are copies of original documents defining:

- the Applicant's legal status
- Product Dossier
- Site Master File (SMF) summary
- Sample products.

UNFPA and its authorized representatives are hereby authorized to conduct any enquiries or investigations to verify the statements, documents and information submitted in connection with this application and to seek clarification from our bankers and clients regarding any financial and technical aspects.

This Letter of Application will also serve as authorization to any individual or authorized representative of any institution referred to in the supporting documentation to provide such information deemed necessary and requested by yourselves to verify statements and information provided in this application or with regard to the resources, experience and competence of the Applicant.

The Applicant declares that all the information provided with the application is valid.

Name of Applicant [Organization] \_\_\_\_\_

Name of Responsible Officer \_\_\_\_\_

Signature \_\_\_\_\_

Position/Title \_\_\_\_\_ Date \_\_\_\_\_

### 1.5 Assessment of documents submitted

The aim of the assessment of the submitted documentation will be to determine whether the applicant/manufacture meets the minimum requirements set out in the relevant ISO standards and *WHO/UNFPA Specification* in respect of product quality and safety, production and quality management, regulatory approval and capacity of production.

UNFPA will attempt to screen the documentation within 30 days of the closing date for responses to ascertain that it contains all the required information. When a submission is incomplete, the manufacturer will be informed and requested to complete the dossier within a specified time period. In the event of noncompliance, the dossier may be rejected and returned to the applicant. Dossiers that are considered complete after administrative screening will be retained by UNFPA for evaluation.

UNFPA will exchange letters with the applicant or manufacturer regarding provisions for confidentiality and the process of assessment of submitted information and to schedule a site inspection. For further information refer to Section 2, Chapter 5 of this document.

## 2 Preparation of a Product Dossier

The Product Dossier follows the requirements included in the *WHO/UNFPA Specification* described in this publication, *WHO/UNFPA TCu380A Intrauterine Devices (IUDs): Specification, Prequalification and Guidelines for Procurement, 2010*.

This chapter is intended to be explanatory and illustrative only. Manufacturers are reminded to consult the cited guidance documents when compiling the Product Dossier.

Each section of the Product Dossier, including attachments and annexes, should be clearly referenced in the table of contents of the Product Dossier. The table of contents should list the sections and sub-sections and then titles in numerical order, with the corresponding page numbers. All pages should be consecutively numbered throughout the document.

### 2.1 Details of products

Provide a list of approved brand names.

For further information refer to:

WHO/UNFPA. *Procedure for assessing the acceptability, in principle, of copper T 380A intra-uterine devices (IUDs) for purchase by United Nations agencies*. Technical Report Series, No. 948. Geneva, World Health Organization, 2008.

### 2.2 Samples

Provide 10 samples of each IUD in its final packaging to enable visual inspection of the product, the packaging materials and the label.

### 2.3 Local, country and regional regulatory approval for the product

List the countries in which:

- the product has been registered and granted a marketing authorization
- an application for marketing authorization is currently pending
- the product has been withdrawn from the market
- any marketing approval has been revoked within the past five years.

### 2.4 Raw materials

List all raw materials, including copper and packaging. Complete the following table.

Add additional explanatory information if required and modify the table as necessary.

Primary materials including copper and plastics		
Chemical name	Manufacturer	Function
Other materials including additives and fillers		
Chemical name	Manufacturer	Function



## 2.5 Supplier(s)

State the name and street address of each facility from which plastic and copper are obtained and where any processing, such as compounding or sectioning into collar-length tubes, is done.

## 2.6 Sites of manufacture

State the name and street address of each facility where *any aspect* of manufacture occurs, including moulding, assembly, production, sterilization, packaging and quality control. Indicate the activity performed at each site.

Provide phone number(s), fax number(s) and e-mail addresses for each site. Include any alternative manufacturers.

## 2.7 Risk management of the product

Provide a Risk Management Plan for the product according to *ISO 14971* and *ISO 13485* standards. Use the latest edition of each standard.

## 2.8 Specifications for finished products

Include the specification for the product, and answer the following questions:

- Does the TCu380A IUD that you currently manufacture meet the requirements of *ISO 7439*?
- Do you manufacture any TCu380A IUD that meets the *WHO/UNFPA Specification*?
- If not, describe the differences between the TCu380A IUD that you manufacture and that which will be produced according to the WHO/UNFPA requirements.

## 2.9 Evidence of compliance with the WHO/UNFPA TCu380A IUD Specification

The following information is required:

- verification that biocompatibility testing has been carried out in accordance with *ISO 10993*, Part 1. See *WHO/UNFPA TCu380A IUD Specification, 2010* for further details of the specific tests required;
- summary reports of biocompatibility testing including, if available, toxicologists' expert reports;

- a narrative description of the tests and acceptance criteria performed at the critical steps in the manufacturing process, the critical process controls and achieved capability (a sampling plan showing where, when and how the samples are taken should be provided);
- data from final release testing of at least three manufactured LOTS made within the past year, to allow a review of the manufacturing process.

The report should be generated for examination by UNFPA. It should be signed by the appropriate authorized person and contain the following information:

- LOT analytical data
- certificates of analysis
- LOT production records, including LOT release test results
- reports of unusual findings, or modifications or changes found necessary, with relevant rationale
- conclusions, with summary process capabilities based on the LOT data.

## 2.10 Test procedures

All test procedures must be described in sufficient detail to allow them to be replicated, if necessary. The results of validations of analytical procedures should be provided, including uncertainty estimates and inter-laboratory comparisons of data quality control comparisons wherever possible.

The range of tests to be conducted should be in accordance with the current *WHO/UNFPA TCu380A IUD Specification*.

## 2.11 Packaging

Packaging materials should comply with *ISO 11607-1 Packaging for Terminally Sterilized Medical Devices. Part 1. Requirements for Materials, Sterile Barrier Systems and Packaging System*.

Provide details of the sources of packaging and specifications of the materials. Alternative packaging

materials can be accepted if their barrier properties and strength are comparable to the recommended packaging and if they meet the requirements of *ISO 11607–2 Packaging for Terminally Sterilized Medical Devices. Part 2. Validation Requirements for Forming, Sealing and Assembly Processes*.

## 2.12 Sterilization

Describe the sterilization process, which must meet the requirements of the appropriate standard for the sterilization method selected:

- *ISO 11135–1. Sterilization of Health Care Products—Ethylene Oxide. Part 1. Requirements for Development, Validation, and Routine Control of a Sterilization Process for Medical Devices*
- *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.*

Include the processes for monitoring and validation of bioburden, validation of the sterilizer and product sterility assurance, with the latest validation reports in each case. Provide copies of the sterilization facility approval certificates.

## 2.13 Shelf-life before insertion

The shelf-life before insertion, known as the Latest Insertion Date of the product must be supported with data from real-time stability studies. Pending the outcome of real-time studies, data from accelerated studies are acceptable. Guidance on conducting stability studies is given in Annex V: Accelerated Ageing Testing.

The shelf-life of the product (Latest Insertion Date) before insertion should be a maximum of five years.

Please note that manufacturers have two years to comply with this testing requirement from the time of publication of this document (December 2010).

The stated shelf-life should be clearly marked on the package as **Latest Insertion Date** (LID). The date of

manufacture must be clearly distinguished from the stated shelf-life.

If the results of real-time studies are not available before the prequalification stage, manufacturers must initiate the studies immediately.

Pending the outcome of the real-time studies, manufacturers may provide data on validated accelerated stability studies at elevated temperatures together with the full method validation report; refer to Annex V.

## 2.14 Labelling and additional information

Provide examples of the labelling that will be used for the sealed pouch, any outer packaging, the inserts and any other information supplied with the device.

## 3 Preparation of a Site Master File (SMF) summary

A Site Master File (SMF) summary must be prepared for each manufacturing site and sent with the letter of application.

The SMF summary should be succinct and, as far as possible, not exceed 25 A4-sized pages.

A SMF summary is a document prepared by the manufacturer from the documented quality management system. It should include the following:

- specific factual information about the manufacturing operations
- quality assurance procedures carried out at the named site
- description of any closely integrated operations at adjacent and nearby buildings.

If only part of a manufacturing operation is carried out at this site, the SMF summary needs to describe only the operations carried out at the site.

A separate SMF is required for every site involved in the manufacturing operation.

Clauses 3.1–3.13, which follow, describe the required content of the SMF summary.

The SMF summary shall have a front title page and a table of contents and shall contain the information described below.

### 3.1 General information

1. name and exact address of the site, including telephone, fax, e-mail, and 24-hour contact telephone numbers;
2. brief information about the corporate structure, including the holding or parent company, affiliates, subsidiaries and partners;
3. total manufacturing capacity of the site, including:
  - moulding
  - assembly
  - packaging
  - sterilization;
4. length of time that TCu380A IUDs have been manufactured at this manufacturing site. Length of time manufacturing TCu380A IUDs at other sites;
5. what other, if any, manufacturing activities take place at this site;
6. summary of type of products manufactured at this site and manufacturing process.
4. a brief summary of the qualifications, experience and responsibilities of key personnel, senior managers and directors, quality assurance supervisors, production manager/director and laboratory manager/director, if appropriate;
5. a summary of policy and procedure for meeting health requirements of personnel engaged in production;
6. a brief description of the staff training scheme, the structure and maintenance of training records, and the policy and method for ensuring verifiable competence;
7. a brief summary of personnel hygiene and safety requirements, including protective clothing;
8. confirmation that there is a written health and safety policy, and a summary of the key components of this policy;
9. information on the use of any outside scientific, analytical or other technical assistance in relation to manufacture and analysis.

### 3.2 Manufacturing certifications

List and provide copies of all relevant certifications, including *ISO 13485* and *ISO 9000* series, if applicable.

### 3.3 Personnel

1. list the total number of persons employed in TCu380A IUD manufacturing;
2. list the numbers employed, by category: senior management, production management, quality assurance, quality control, maintenance and administration;
3. an organization chart showing all management and supervisory positions, including arrangements for quality assurance and quality control;
- 3.4 Premises and equipment
1. a simple plan or description of the manufacturing areas with an indication of scale (architectural or engineering drawings not required);
2. a brief description of the nature of the construction and finishes of floors, ceilings, and walls;
3. a brief description of ventilation systems, including steps taken to prevent product contamination and excessive exposure of staff to dust and other substances;
4. a brief description of water systems, including sanitation and effluent treatment; schematic drawings of the systems are desirable;
5. a concise description of planned preventive maintenance programmes for the premises, equipment and any recording system;

6. a brief description of the main equipment used in production and control laboratories, including major computer systems used for production and quality control (a full list of equipment is not required);
7. a brief description of qualification and calibration procedures, including arrangements for validating computerized systems and accreditations, for external laboratories providing traceable calibrations;
8. confirm availability of written specifications and procedures for cleaning manufacturing areas and equipment;
9. a brief summary of the procedures for monitoring and controlling microbiological contamination in production areas and of the product, and procedures for controlling the purity of the air and water.

### **3.5 Documentation**

Describe briefly arrangements for preparing, revising and distributing all necessary management system documentation.

### **3.6 Records**

Describe briefly arrangements for the safe storage and retrieval of records.

### **3.7 Production**

1. a brief description of production operations, using, whenever possible, flow sheets and charts; specify important parameters; include a brief description of the scale of production; identify equipment by type (e.g. testing machines); and state working capacity, where relevant;
2. a summary of the procedures for handling starting materials, work in progress, packaging materials and finished products, including sampling, quarantine, release and storage;
3. a brief description of arrangements for handling rejected materials and products;
4. a brief description of the general policy for process validation and a summary of the validation plan.

### **3.8 Risk management plan**

A summary of the risk management assessment undertaken in accordance with *ISO 14971* and the resulting risk management plan.

### **3.9 Quality control**

1. a brief description of the quality control system and of the activities of the quality control department;
2. a brief description of the sampling and testing procedures for in-process testing and final product release, including pass/fail criteria.

### **3.10 Distribution, complaints and product recall**

1. a brief description of the arrangements and recording system for distribution;
2. a brief description of the arrangements for handling post-production monitoring and vigilance reporting, complaints and product recalls.

### **3.11 Self-inspection (internal audits)**

A brief description of the self-inspection (internal audit) system.

### **3.12 Corrective and preventive action**

A brief description of procedures and arrangements for identifying the need for and for implementing corrective and preventive action.

### **3.13 Design and development**

A brief description of procedures used to control design and development.

## **4 Scope of manufacturing site inspection**

### **4.1 Introduction**

The objectives of the manufacturing site inspection are to:

- determine that TCu380A IUDs are consistently manufactured to the required specifications;
- verify whether the production processes occur as described in the Product Dossier and Site Master File summary.

UNFPA will plan and coordinate inspections at the manufacturing sites to assess the manufacturing process, the product and the quality management system for compliance with the general and performance requirements of the *WHO/UNFPA TCu380A IUD Specification* and Good Management Practice (GMP) as set out in, but not limited to, the latest editions of the following international standards:

- *ISO 7439. Copper-Bearing Intra-uterine Contraceptive Devices—Requirements, Tests.*
- *ISO 13485. Medical Devices—Quality Management Systems: Requirements for Regulatory Purposes.*
- *ISO 14971. Medical Devices—Application of Management to Medical Devices.*
- *ISO/IEC 17025. General Requirements for the Competence of Testing and Calibration Laboratories.*
- *ISO 10993–1. Biological Evaluation of Medical Devices. Part 1. Evaluation and Testing.*
- *ISO 11135–1. Sterilization of Health Care Products—Ethylene Oxide. Part 1. Requirements for Development, Validation, and Routine Control of a Sterilization Process for Medical Devices*
- *ISO 11737–1. Sterilization of Health Care Products—Radiation. Part 1. Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices.*
- *ISO 11737–2. Sterilization of Health Care Products—Radiation. Part 2. Establishing the Sterilization Dose.*
- *ISO 11607–1. Packaging for Terminally Sterilized Medical Devices. Part 1. Requirements for Materials, Sterile Barriers and Packaging Systems.*
- *ISO 19011. Guidelines for Quality and/or Environmental Management Systems Auditing.*

The inspection will be performed by a team of inspectors, consisting of experts appointed by UNFPA, who will act as temporary advisers to UNFPA. The inspectors must have documented qualifications: expertise in TCu380A IUD manufacture, auditing and quality management and specific experience in inspecting IUD manufacturing sites.

Information submitted in response to the invitation for an Expressions of Interest (EOI) and the assessment report will be made available to the inspectors. The inspectors will comply with the UNFPA rules on confidentiality and conflict of interest, as described in Section 2, Chapter 5 of this document and the *WHO/UNFPA Procedure for Assessing the Acceptability, in Principle, of TCu380A for Purchase by United Nations Agencies*, WHO, May 2008.

## 4.2 Inspection guide

The following table is a guide for inspecting manufacturing sites. It lists the key areas to be reviewed during the inspection. IUD manufacturing sites vary widely in size and scale, equipment and processes, and inspectors will have to use their expertise and knowledge of IUD manufacture to adapt the table to the specific situation at each site. Each team will perform the inspections and report its findings to UNFPA in accordance with the standard operating procedures (SOPs) established by UNFPA to ensure a standardized, harmonized approach.

The areas listed in Table 6 are those that will usually be covered during an inspection but may vary for different process flows and use of different materials. Access to all of the applicant/manufacture's documents and records will be required. A detailed inspection checklist will be available as an SOP for use by the inspectors. Table 6 indicates the areas that are subject to inspection.

**Table 6. Inspection guide**

Areas under inspection	Comments
<b>1. General company details</b>	
Address and contact details	
IUD designs manufactured	
Independent certification of systems and products, including regulatory approvals	
Markets supplied	
Operating hours and shifts	
<b>2. Management team and key staff</b>	
Management team and key staff, including authority and responsibilities	
Organization chart	
Out-of-office hours arrangements, responsibilities and authority	
<b>3. Human resources</b>	
Staff numbers and areas of deployment	
Job descriptions	
Staff selection, induction and training systems	
Records	
<b>4. Production capacity throughout the operation</b>	
Number and type of machines	
Quoted output and yields	
Actual sales in past three years	
Product realization and planning	
<b>5. Raw materials</b>	
Purchasing	
Selection, storage and quality	
Vendor evaluation and validation	
Acceptance and storage procedures	
Status indication, labelling and documentation	
Environment	

Areas under inspection	Comments
<b>6. Preparation of compounded materials</b>	
Where undertaken	
Process	
Testing and controls	
Documentation and labelling	
Environment	
<b>7. Moulding</b>	
Materials used	
Sourcing	
Process	
Process validation	
Process controls and monitoring	
Environmental and personnel hygiene controls	
Production quality control	
Production bioburden validation	
Identification, traceability and status	
Storage and disposition of non-conforming and rejected goods	
<b>8. Assembly</b>	
Equipment	
Process	
Process and equipment validation	
Process controls and monitoring	
Environmental and personnel hygiene controls	
Product quality control	
Product bioburden validation	
Identification, traceability and status	
Storage and disposition of non-conforming and rejected goods	
<b>9. Provisions for storage and control of work in progress</b>	
Segregation	
Labelling	
Status identification	
Environment	
Security	



Areas under inspection	Comments
<b>10. Packaging</b>	
Materials used	
Process	
Adequacy of equipment	
Testing and controls	
Documentation and labelling	
Understanding of LOT coding	
Equipment and process validation	
Environment	
<b>11. Sterilization</b>	
Where undertaken	
Methods used	
Testing and controls	
Sterilizer validation	
Product sterility validation	
Documentation and labelling	
<b>12. Warehousing</b>	
Adequacy	
Segregation	
Labelling	
Stock control and rotation	
Presence of aged or non-conforming goods	
<b>13. Distribution procedures</b>	
Agreements	
Records	
<b>14. Quality control plan</b>	
Details of product testing at each stage of manufacturing process, including LOT release	
<b>15. Outgoing product quality</b>	
Verification of compliance of product and process capability	



Areas under inspection	Comments
<b>16. Quality system and documentation</b>	
Quality policy and objectives	
Quality manual	
Standard operating procedures (SOPs) and work instructions (WIs)	
Documented versus actual practices	
Document control	
Process approach	
Contract review	
Risk management	
Validation policy and management	
Complaints, recall, vigilance and advisory notices	
Post-market surveillance	
Audit	
Control of non-conforming product (corrective and preventive action)	
LOT traceability	
Statistical analysis of collected data	
Product master file	
Management review	
Improvement	
<b>17. Maintenance</b>	
Documented programme, including schedule	
Details of maintenance for key areas and records	
Adequacy of programme monitoring and effectiveness assessment	
<b>18. Laboratory facilities, competence and calibration</b>	
Routine activities of each laboratory	
Equipment and methods	
Reporting of results and documentation	
Calibration system	
Certifications	
Participation in inter-laboratory trials	
Research and development	
Understanding and competence	

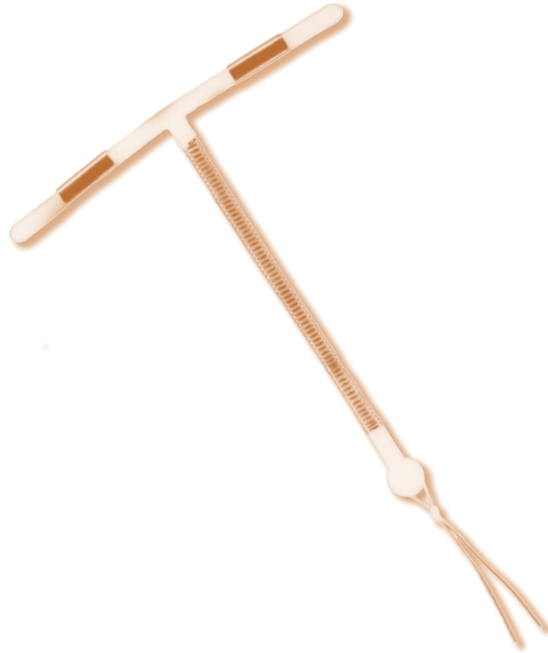
Areas under inspection	Comments
<b>19. Shelf-life and stability</b>	
Detail of studies conducted	
Retention sample programme	
<b>20. Buildings, grounds and services</b>	
Buildings and premises	
Clean-room particulate count	
Overall fabrication and condition of premises	
Pest and rodent control	
Compressed air	
Electricity	
<b>21. Prequalification independent testing</b>	
Sampling	
Results summary	

### *References*

1. *Procedure for assessing the acceptability, in principle, of copper-bearing TCu 380A intrauterine devices (IUDs) for procurement by United Nations agencies, Annex 3.* WHO Technical Report Series, No. 948. Geneva, WHO, May 2008.
2. *WHO Expert Committee on specifications for pharmaceutical preparations.* Technical Report Series, No. 948. Geneva, WHO, May 2008.



**SECTION THREE**  
**GUIDELINES FOR PROCUREMENT**



**CHAPTER 7**  
**Guidelines for Procurement**



## SECTION THREE

### CHAPTER 7: GUIDELINES FOR PROCUREMENT

#### 1 Introduction

An effective supply chain ensures that the right quality product, in the right quantities, and in the right condition is delivered to the right place at the right time, for a reasonable cost. To accomplish this, the customary supply chain process has four major sub-components, each focused on one aspect related to the product:

- product selection
- product procurement
- product distribution
- product use.

Section 3 of this manual addresses the procurement component of the supply chain cycle, identifying the key procurement steps used to enable reproductive health care programmes to receive good-quality essential medicines, including contraceptives, that meet the needs of their clients.

This can be achieved, however, only if the right policies are in place, sufficient budget has been allocated, and viable systems are in place that support improved access to and use of the commodity. The UNFPA Reproductive Health Commodity Security (RHCS) programme is a global programme involving governments and international organizations committed to working collaboratively to create comprehensive strategies focused on attaining the goal that: “every person is able to choose, obtain, and use contraceptives and other essential reproductive health supplies whenever she or he wants and/or needs them”.

The *WHO/UNFPA TCU380A IUD Specification and Prequalification Scheme, 2010*, together with the key principles of the procurement process outlined in this chapter, will make a valuable contribution towards ensuring improved access to a contraceptive device that has been proven to be safe and effective.

Improved access to contraceptives can only be achieved if systems are established to support the procurement of good-quality products, as detailed in this manual. At the same time, effective procurement processes must be part of a broader strategic and co-coordinated effort

to improve access to and the use of reproductive health essential medicines and contraceptives.

#### 1.1 Procurement

These guidelines outline the steps required in the procurement process to enable country programmes to receive good-quality contraceptives, including the TCU380A IUD. It will focus on the procurement of the TCU380A IUD, as related to the prequalification process outlined in this manual, but the principles can be applied to any product.

Detailed methodologies for conducting the public-sector procurement process and managing the supply chain have been developed by a number of international agencies working in the field of contraceptive procurement and logistics management<sup>1</sup>.

To ensure that the procurement steps outlined in this manual are harmonized with the latest guidance, the 10-step approach to procurement summarized in this document is based on the *Procurement Capacity Toolkit: Tools and Resources for Procurement of Reproductive Health Supplies*, published by PATH in 2009. This toolkit synthesizes the public-sector supply process for reproductive health commodities into three phases: *programme planning, procurement process, and performance*. Within these three phases, 10 essential steps are identified that are designed to support the implementation of the process required to procure a good-quality product at a reasonable cost at the time needed.

The three phases and 10 steps of public-sector health care procurement are identified in Table 7, next page.

#### It should be noted that:

- a) The steps outlined in this manual define effective practice, but the actual procurement process that a purchaser follows will vary slightly, depending on such factors as government procurement

<sup>1</sup> John Snow Inc., FHI, Crown Agents, Population Services International (PSI), UNFPA, PATH, and the World Bank have developed technical resource materials on establishing and strengthening the various components of the supply chain and ensuring product quality assurance.

regulations, source of funding, whether qualified manufacturers exist in-country, and the purchaser's own procurement procedures and requirements.

- b) Although the procurement steps have been presented in a sequential format, it is often necessary to implement several steps at the same time.

- c) Procurement steps may vary from country to country, but, to be undertaken effectively, each step requires:
- leadership
  - adequate human and financial resources
  - willingness to collaborate and coordinate with the different parties involved in each step of the procurement process
  - timely decision-making.

Table 7. Three phases and 10 steps of procurement	
Phases	Ten steps of procurement
<b>1 Programme planning</b>	1. Define supply requirements 2. Customize the specification 3. Assess procurement options 4. Budget, funding and procurement requisition
<div>↓</div> <b>Critical link: funded procurement requisition</b>	
<b>2 Procurement process</b>	5. Procurement planning 6. Develop Bidding Documents and inviting offers 7. Select suppliers 8. Contract negotiation/award
<div>↓</div> <b>Critical link: signed contract and payment guarantee</b>	
<b>3 Performance</b>	9. Contract performance and monitoring 10. Delivery of goods
<div>↓</div> <b>Critical conclusion: delivery and acceptance of good-quality products</b>	

The rest of this chapter on procurement is organized according to these 10 steps.

## **Ten steps in the procurement process**

### **Phase 1: Programme planning**

#### **1 Step 1: Define supply requirements<sup>2</sup>**

Assessing and defining contraceptive requirements depends on several factors that should be discussed with all parties involved in usage, promotion, procurement and distribution of the TCU380A IUD.

##### ***1.1 Define programme context***

Before forecasting and quantifying product requirements, it is important to understand the needs of the intended end-users and the history of TCU380A IUD procurement and use in the country.

This information can be obtained through a desk search of available information and by meeting with all parties involved in the programming, procurement, distribution and promotion of contraceptives.

There is a need to determine:

- Which agencies, donors, nongovernmental organizations, social marketing agencies, commercial enterprises and different public-sector ministries are involved in the procurement, distribution and promotion of contraceptives, including the TCU380A IUD?
- What are their roles?
- What are the sources of funding?
- What sources of supply are used?
- How are the contraceptives, including TCU380A IUDs, procured and in what quantity?

It is important to create a broad picture of what is happening in the field of contraceptive procurement, including TCU380A IUD programming and procurement, in the country to ensure that all stakeholders who need to be involved in the process are identified.

<sup>2</sup> For additional information see Module 1 of the *Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies* (PATH, 2009).

#### ***1.2 Forecast programme requirements***

Before the actual procurement process can begin, it is important to know the quantity of contraceptives, including TCU380A IUDs, to be ordered and the desired delivery schedule. Questions that need to be answered by the procurer and the programme managers are:

##### *Users and use*

- Who are the intended end-users?
- What research, if any, has been undertaken to determine the population's current needs and unmet needs?
- What are the trends in contraceptive use and plans for promotion of TCU380A IUDs?
- Are there expected policy, programmatic or other changes that will affect this trend?

##### *Current programming and supplies*

- Which programmes will this procurement supply? (Combining procurements for several programmes, such as those from HIV/AIDS and reproductive health, may offer savings through price discounts for quantity. Also, combining procurements reduces the purchasers' administrative costs that would be associated with processing multiple orders.)
- What is the current stock of contraceptives, including TCU380A IUDs, at those programmes?
- When will the products either reach their expiry date or, for TCU380A IUDs, Latest Insertion Date (LID)?
- Are there any products that may not be distributed before they reach expiry?
- Are losses or transfers in or out of programmes expected?
- How many months will supplies last?
- What is the annual consumption?
- Are orders or shipments already planned or in transit for the programme?
- What is the desired buffer stock level that the programmes want to maintain?



- What is the storage capacity for contraceptives including TCU380A IUDs? (Limited storage capacity could require that the procurement of contraceptives be phased in smaller shipment increments over time rather than arriving as one large consignment.)
- Are the storage facilities secure and adequate for the long-term storage of contraceptives including TCU380A IUDs?
- Does the storage facility provide adequate protection against excessive temperature rises and other environmental issues?
- Is there a Logistics Management Information System (LMIS) in place that captures stock levels and distribution to users?

#### *Current procurement process*

- What are the requirements of the national regulatory authority (or authorities) regarding the procurement and importation of contraceptives, including TCU380A IUDs, that may be classified as a medical device?
- How are contraceptives, including TCU380A IUDs, imported into the country? (Airfreight is generally very expensive, and so they are usually shipped by sea to the nearest port of entry.)
- What is the history of previous shipments?
- What problems, if any, have been encountered with the procurement and distribution of contraceptives, including TCU380A IUDs, over the last two years?
- What is the average length of time involved in the procurement cycle? (This may vary according to the source of funds, but it is important to consider this issue when forecasting the demand for contraceptives, including TCU380A IUDs. It can take between 12 and 18 months to complete a procurement cycle.)

Information gathered by undertaking this assessment will enable the purchaser to identify the total quantity of TCU380A IUDs and other contraceptives required to meet programme needs.

Different methods can be used to estimate requirements, depending on the time frame to be projected, the geographic area covered, the purpose of the forecast, and the availability of data to develop the forecast. Forecasting methods use logistics data (including consumption data, service statistics and population data).<sup>3</sup>

Forecasts are made using more than one method and then compared and reconciled. This is done because usually data are not adequate to rely on one method alone and because different methods have different advantages. Consolidating forecasts from different data sources improves the accuracy of the overall forecast.

For additional information on forecasting, see also: *The Contraceptive Forecasting Handbook for Family Planning and HIV/AIDS Prevention Programs* (John Snow Inc., Family Planning Logistics Management Project, 2000). This is a reference book for forecasting commodity needs for family planning and HIV/AIDS prevention programmes. Topics range from general methodological considerations to special considerations when forecasting for HIV/AIDS prevention programmes.

## **2 Step 2: Customize the specification**

### ***2.1 Review the WHO/UNFPA TCU380A IUD Specification (see Section 1, Chapter 2)***

A specification is a statement of a buyer's requirements. One of the more important responsibilities of a purchaser is to ensure that the TCU380A IUD specification is accurate, detailed, clear and consistent.

The purchaser should review the WHO/UNFPA TCU380A IUD Specification to fully understand the different levels of requirements detailed in the specification and to identify which requirements can be adapted by the purchaser to address specific programme needs and which requirements must be left unaltered so as not to jeopardize the integrity and quality of the product. The scope for customization in the *WHO/UNFPA TCU380A IUD Specification* is limited to accessories. The *WHO/UNFPA TCU380A*

<sup>3</sup> Summary information on these methods can be found in Module 1 of the *Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies* (PATH, 2009).

*IUD Specification* can be copied from this document or the WHO web site: <http://www.who.int/rhem/prequalification/9789241500999/en/index.html>.

### 3 Step 3: Assess procurement options<sup>4</sup>

In preparing for the procurement of contraceptives including TCU380A IUDs, the purchaser must determine which option, or procurement method, would be most appropriate for the particular circumstances. The process of assessing the options is intended to:

- identify the procurement options that are possible
- consider what is practical under the circumstances
- look at who can/will do the work
- examine cost implications
- evaluate the options and select the most appropriate option, or procurement method, for the procurement.

The assessment process must be objective and must look to answer questions such as:

- Are there any issues that might affect the purchaser's ability to perform a specific procurement method?
- Does the purchaser have staff with the knowledge and skills required for implementing a more complex procurement method such as international competitive bidding?
- What is the value of the order, and is it large enough to attract bids from major international suppliers?
- What method is most cost-effective for the purchaser?
- Does the purchaser have suitable infrastructure, such as access to foreign currency, international banking and Internet services?

- Is sufficient time available to conduct a more complex procurement method such as international competitive bidding?
- Are there funder's requirements specifying that a certain procurement method be used?

#### 3.1 Select a procurement method

Upon completion of the assessment process, the purchaser should have sufficient information to determine which procurement method would be most appropriate for the particular circumstances. In principle, there are four common procurement methods that the purchaser could choose from.

##### 3.1.1 Procure directly from a prequalified manufacturer through a competitive bidding process

This is a satisfactory method for fairly large orders. When undertaking this method of procurement, it is important that procurement staff have the technical skills needed to follow the procedures detailed in these guidelines.

Competitive bidding, including international competitive bidding, is the most complex of the procurement methods used. It is the method preferred by some international lending organizations, such as the World Bank. The purchaser must (a) develop the specification and Bidding Documents; (b) either select prequalified potential suppliers from the WHO/UNFPA list or undertake a comparable prequalification process; (c) implement the bidding process; (d) select the supplier(s); and (e) arrange for shipment.

Unless the purchasing entity has existing procurement capacity with competitive bidding experience, this method may not adequately support the needs of the programmes.

In addition, the time required to complete an international competitive bidding process (from identification of requirements to delivery of product) can be quite lengthy, possibly ranging from 12 to 18 months.

Purchasing entities that select this method must ensure that they comply with and perform every required step in the process as identified by both national procurement policies and donor requirements. If the procurement is donor-funded, the purchasing entity

<sup>4</sup> For additional information see Module 3 of the *Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies* (PATH, 2009).

should secure an agreement with the donor to use WHO/UNFPA prequalified suppliers. The WHO/UNFPA Prequalification Scheme is harmonized with the WHO Prequalification Scheme for Essential Medicines. A list of prequalified manufacturers is available for use by any procuring entity; refer to <http://www.unfpa.org/public/procurement/>; <http://www.unfpa.org/webdav/site/global/shared/procurement/Prequalified%20IUD%20Factories%20Feb%202010.pdf>; or <http://www.who.int/rhem/prequalification/9789241500999/en/index.html>.

### **3.1.2 Source from a procurement agency**

Procurement agencies undertake sourcing for organizations and national programmes that do not have their own procurement department and/or staff with expertise in contraceptive procurement and/or the time to develop the needed capabilities to conduct competitive bidding.

Although independent procurement agencies exist in most major cities worldwide, very few of them have extensive knowledge of and experience with the special requirements for buying contraceptives, including TCu380A IUDs. It is, therefore, important to select a procurement agent with a track record of procuring good-quality contraceptives, including TCu380A IUDs.

The procurement agent takes responsibility for procurement and quality assurance of the product. The purchaser has to review and adopt the *WHO/UNFPA Specification* and issue a suitable contract to the procurement agent. The agent will be responsible for ensuring that potential suppliers are prequalified by WHO/UNFPA, selecting the supplier, awarding the manufacturing contract and arranging for shipment. It is recommended that all procurement agents use WHO/UNFPA prequalified suppliers.

Some procurement agents may have existing supply contracts with prequalified TCu380A IUD manufacturers and so may be able to offer a purchaser a shorter delivery time. For small orders arrangements can be made with an agent to purchase the quantity required as part of a larger bulk order. This can reduce procurement costs.

If no local agency has experience with purchasing contraceptives, including TCu380A IUDs, it is

advisable to use an international procurement agency that does (see Clause 3.1.3, below). For example, UNFPA, IPPF/ICON, Marie Stopes International (MSI), Crown Agents, Population Services International (PSI), and John Snow, Inc. (JSI) all act as international procurement agents for contraceptives. They will undertake the procurement process and/or, if funds are available, may provide technical assistance to support the procurement process.

### **3.1.3 Source from an international procurement agency/organization**

International agencies such as UNFPA, USAID, IPPF/ICON, MSI, PSI, and others provide contraceptives, including TCu380A IUDs, for sale or donation to country programmes. Unique programme requirements can be considered if the quantity ordered is significant and there is sufficient time for a manufacturer to process the order.

This is an option for organizations and national programmes that do not have the procurement capacity required to implement more complex procurement methods, such as sourcing directly from a TCu380A IUD manufacturer through a competitive bidding process or using a procurement agency. Depending on the quantity of TCu380A IUDs needed, this option can also offer a shorter delivery time than the other options.

Certain international organizations, such as UNFPA and USAID, maintain stocks of contraceptives, including TCu380A IUDs, to respond quickly to stock-outs and emergency situations. These

Procurement should not be through a non-specialized commercial agency or importer because the TCu380A IUD may not be prequalified and may not be traceable to the manufacturer. Thus, quality issues will prove more difficult to resolve.

WHO recommends the use of an experienced procurement agency and that the source of the contraceptives/TCu380A IUDs be a WHO/UNFPA prequalified primary manufacturer.

organizations can draw upon supplies either held in stock or obtained from manufacturers, based on their pre-existing supply contracts, and they will either sell or donate to programmes for distribution in-country.

### 3.1.4 Buy from a social marketing organization

Social marketing organizations, such as PSI, DKT and MSI, operate much like commercial retail companies. They buy products and promote and sell them in the market, but at subsidized prices. Occasionally, a programme may approach a social marketing

organization in a country, requesting TCu380A IUDs. If the social marketing organization has sufficient stock, it may sell or donate some to the requesting programme. While not a common source of procurement, this is another avenue that country programmes can explore.

Table 8 compares the advantages and disadvantages of the four basic procurement methods. Once the procurement method is decided, it should become a routine practice to then inform the budget and/or finance committee of the method selected.

Table 8. Comparison of four procurement methods			
Method	Experience and capacity of programme staff	Size of procurement	Advantages/disadvantages
<b>Direct from manufacturer</b>	Programme must have adequate staff with appropriate skills, particularly an experienced procurement manager.  Alternatively, expert technical assistance should be sought to help develop local capacity of the logistics management chain.	Better for larger procurement cycles.	Good control of supply and quality assurance.  Requires reliable staff and experienced management.
<b>Procurement agency</b> (do not use a non-specialized commercial agent)	Valuable where capacity of the in-country logistics management requires support or further development.	Good option for large, more complex procurements.  May be expensive for smaller quantities. It may be possible for the purchase of smaller quantities to be combined with an existing supply contract. This would reduce costs.	Important to collaborate with the procurement agent to ensure procurement to the correct specification and within an agreed-upon time frame. Can be used to develop the capacity of the logistics management chain.  Important to select a procurement agent with a reputation for following quality assurance measures in a timely fashion.  The procurement agent charges a fee for its services.
<b>International agency</b>	No experience required.	Good option for large volumes.	Quality management and control over supply chain assured. Very competitive prices. Long-term agreement with suppliers (quality monitored over time). Capacity to respond to requests quickly. Assistance can be provided to develop the capacity of the logistics management chain.  The international procurement agency charges a fee for its services.
<b>Social marketing organization</b>	Complete procurement and marketing and distribution service.	More suitable for working in larger markets.	All details of procurement handled by outside agency. Complete procurement, marketing and distribution service.

Source: *World Bank medical device procurement guide*. Washington, D.C., World Bank, November 2001.

#### 4 Step 4: Budget, funding and procurement requisition<sup>5</sup>

Given the often limited financial resources that are available for funding reproductive health commodities, it is important that the process of estimating product costs, developing budgets and securing funding be conducted in as effective a manner as possible. Accurately estimating procurement costs is an important first step in this process.

##### 4.1 Estimating procurement costs to determine a budget

There are several cost factors that must be considered when developing a budget estimate for procurement of contraceptives, including TCu380A IUDs, that is then used to secure funding. The key procurement cost factors include:

- *Unit price.* The unit price charged by the manufacturer or supplier constitutes the largest component of the TCu380A IUD procurement cost. There are several methods that a purchaser can use to estimate the unit price. Direct enquiry to the manufacturer or supplier and previous contract invoices are useful sources for price information. Since the quantity procured can influence unit price, it is important, when contacting manufacturers or reviewing previous invoices, to factor in the estimate of programme quantity developed in the preceding step. It is also important to make clear to the manufacturer or supplier that the information requested is for a budget estimate only and there is no commitment being made by either party.

Another resource for price information is the Management Sciences for Health (MSH) International *Drug Price Indicator Guide*, available online at: <http://erc.msh.org>. This guide provides prices from suppliers and procurement agencies as well as prices paid by government agencies. It is important for the purchaser to review the “Data Notes” page, which provides information about sources and how prices were

calculated. UNFPA Procurement, Copenhagen, also can provide an estimate of current prices.

- *Freight cost and insurance.* The estimated costs to ship TCu380A IUDs and insure them during transit must also be included in the budget estimate for procurement. These costs are often included in the unit cost. Therefore, it is important for the purchaser, when directly enquiring from a manufacturer, reviewing previous contract invoices or conducting Internet research, to review the stated INCOTERMS (shipping terms) to determine the extent to which freight costs and insurance are included in the unit price.

If the unit price does not include freight and insurance costs, the purchaser can request an estimate of these costs from a freight shipping agency. This would require providing the weight and dimensions of the shipment, the mode of transportation (ocean, air or ground) and the value of the shipment. When this information is not readily available, purchasers will often add a standard percentage to the value of the goods. For example, for shipping and insurance costs UN agencies estimate 15% of the value of the goods purchased.

- *Import/customs clearance costs.* These vary from country to country and port to port. Therefore, the purchaser must enquire locally to establish reasonable cost estimates for import licence fees, customs broker fees and port clearing fees.
- *Post-shipment confirmatory testing.* If national regulations call for confirmatory testing of TCu380A IUD (LOTS), then these costs should also be included in the budget estimate for procurement. The purchaser must enquire locally to find out whether there is a specific country regulatory requirement. **WHO recommends that only one accredited laboratory carry out testing.**
- *Taxes.* Most public-sector health commodities are exempt from tax. This is not always the case, however, and sometimes value-added tax is applied uniformly to all products. The purchaser must enquire locally to determine if there are

<sup>5</sup> For further information on budgeting and funding, see Module 4 of the *Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies* (PATH, 2009).



any taxes that should be included in the budget estimate for contraceptives including TCU380A IUD procurement.

The above costs are directly associated with procurement and the related activities required to ship and clear the product through customs. They become the budget estimate that is used to secure funding.

There are, however, additional costs that are associated with the contraceptive/TCU380A IUD programmes that are not directly related to procurement.

Programme staff must be fully aware of these other costs to ensure that they are adequately addressed in their overall programme budget. These in-country programme costs include:

- promotion costs
- warehouse and storage costs
- distribution and transportation costs.

Establishing and maintaining an open communication channel between the purchaser and the programme staff will help ensure that contraceptive procurement costs and programme costs are accounted for and appropriately budgeted.

#### **4.2 Funding**

Funding for health care commodities, including contraceptives, for public-sector programmes in low-resource countries has historically been limited and insufficient to meet full health care programme requirements. This shortfall has been addressed primarily through funding support and donations from multilateral organizations such as the Global Fund for AIDS, TB and Malaria; UNFPA; and the World Bank and through bilateral donors such as USAID, the UK Department for International Development (DFID), Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) and other agencies.

In the last decade, however, there has been a trend towards providing donor funding through arrangements such as Sector-Wide Approaches (SWAs) and basket funding, in which the international agencies pool their financial resources and transfer funds to the government to use to implement the health care

programme that has been negotiated between the partnering international agencies and the host national government. In many of these financial arrangements, the partnering international agencies will require the host national government to establish a national budget line for reproductive health essential medicines and commodities, including all contraceptives, as a first step towards the government eventually taking full responsibility for funding these items from the national budget. Additionally, under SWA arrangements the national government is often assigned responsibility, with review, oversight and technical support provided by the SWA partners as appropriate, for procuring the health care commodities funded under the programme.

In most cases the programme supply requirements under a SWA or basket-funded approach are negotiated between Ministry of Health and Finance managers and representatives of the international agencies and donor countries. The purchasing entity's role, in consultation with other contraceptive programming experts, is to provide the budgetary information and programmatic justification to inform the negotiations. As part of the negotiation, each party must agree on the terms and conditions that govern the procurement, quality control, importation and distribution of these contraceptives, including TCU380A IUDs.

Bilateral donor funding for contraceptive procurement is usually initiated by senior ministry personnel contacting the donor's country mission with a request for support. Many countries may already have arrangements in place that are renewed on an annual basis. For bilateral donor funding requests, the purchasing entity's role is generally limited to providing senior government personnel with specific programme and cost information.

For contraceptive procurement funded through the national government, the purchaser must submit accurate estimates of the contraceptive procurement budget for government approval.

In each of the above funding scenarios, it is important to make allowances for the length of time it will take to secure funding. It is also important to determine what kind of payment mechanism will be used.

The completion of the budget and funding process should result in an official procurement requisition that identifies the products to be procured, the quantities, the amount of funds authorized for the procurement and other important details necessary to implement final planning for the procurement.

## Phase 2: Procurement process

### 5 Step 5: Procurement planning<sup>6</sup>

The procurement planning and scheduling process is an important step because it:

- provides a framework for guiding procurement activities and monitoring progress;
- provides an opportunity to anticipate problems and solve them before they occur;
- establishes expectations for a delivery date that other parties will use for their own planning purposes;
- establishes a time frame for payment obligations.

For a procuring entity to be able to successfully implement a procurement plan, it needs a defined chain of authority to support and validate its actions, a clear definition of where its responsibility begins and ends, and an understanding of the supply chain process to know whom to contact for information on activities in the supply chain that are outside its mandated performance area.

The procuring entity also must be authorized to contract and commit funds on behalf of the organization that it represents. A formal delegation of financial powers is used for this purpose in some government structures.

As part of the process to develop a procurement plan, the procuring entity should:

- confirm budget allocations and timing for availability of funds by directly contacting the appropriate funding authority;

- review technical specifications to make sure that they are complete and in a format consistent with international standards for the industry, making sure that:
  - the general, performance and design description is complete
  - regulatory and testing requirements are clearly stated
  - packing, labelling and marking requirements are included
  - sampling, inspection and testing protocols are included;
- confirm that the delivery date, location and mode of transport are appropriate;
- confirm that the date of delivery is realistic;
- confirm that specific country requirements and national regulatory procedures have been taken into consideration. (These issues are discussed in more detail in the following section.)

### Country requirements

Since TCu380A IUDs are medical devices, many countries have special regulations covering their importation and distribution. Any procuring entity involved in the procurement of TCu380A IUDs for a particular country must be aware of these rules and regulations. Questions concerning specific requirements that should be answered include:

- Is there a mandatory national quality standard with which all TCu380A IUDs must comply?
- How are the standards applied?
- What other entry requirements are there, such as import duties and certification?
- Is there a requirement for registration prior to importation?
- Is there an in-country requirement for confirmatory testing?

Familiarity with these regulations will help to ensure compliance with national requirements, which will enable the smooth clearance of the TCu380A IUDs

<sup>6</sup> For further information on procurement planning see Module 5 of the *Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies* (PATH, 2009).



through customs and reduce frustrating delays that can hold up delivery after the products have arrived in-country. Information on current regulatory requirements for TCU380A IUDs can be obtained from the National Regulatory Authority (NRA) of each country. The role and responsibilities of a National Regulatory Authority are briefly discussed in the following section.

#### *National Regulatory Authority (NRA)*

The National Regulatory Authority (or Drug Regulatory Authority) in every country undertakes some type of licensing or registration process to protect the population from unsafe or ineffective pharmaceuticals, contraceptives, and medical devices. National Regulatory Authorities bar unlicensed products from entering their countries and look to national customs services for enforcement. Many countries do regulate the importation of TCU380A IUDs, and so it is important to check the local regulations. Regulatory licensing procedures can be complex, lengthy, and expensive for the manufacturer, so those without an existing presence in a country are reluctant to begin the process unless a contract is assured. Given the time that it can take for licensing, this issue threatens timely delivery and limits competition.

Procurement officers must communicate with National Regulatory Authority personnel in order to obtain accurate information about registration requirements that should be included in Bidding Documents. They also need to stay current on products that are registered in-country and ensure that procurement specifications reflect current regulatory requirements. In addition they must determine if the NRA requires confirmatory testing of the product once it is received in the country. The procedure for confirmatory testing including who pays the cost of such testing should be clarified and included in the contract.

If procurement personnel know from experience that there may be problems and/or delays due to budget

Always meet with representatives from the national regulatory authority and customs to discuss their requirements early in the procurement process.

deficits, mode of transportation, or importation challenges, these issues should be discussed and solutions sought during the procurement planning phase.

After gathering the necessary information described above, the procuring entity develops a detailed procurement plan, with clear timelines and delegation of responsibility for each activity identified in the plan, along with a clear process for monitoring implementation of the plan.

#### **6 Step 6: Developing Bidding Documents and inviting offers<sup>7</sup>**

In public-sector competitive procurement, the purchasing entity prepares and provides detailed Bidding Documents to potential suppliers. These documents explain all the requirements of what is to be supplied, all rules and procedures for bidding, and specific criteria that will be used to choose a winning bid. Some sections of the Bidding Documents become part of the future contract between the supplier and the purchaser.

Make sure Bidding Documents are correct and complete in every way because, under the rules of public procurement, nothing can be changed after bids are opened, even if a mistake is discovered.

Well-prepared Bidding Documents and process:

- vastly reduce problems during the procurement process concerning bidding, evaluation, and contract award;
- provide a key opportunity to protect against counterfeit, fake, and possibly unsafe products;
- set rules and expectations for contract performance, including timely delivery of the product;
- define responsibilities of the purchaser and the eventual supplier.

<sup>7</sup> For further information on the preparation of Bidding Documents, see Module 6 of the *Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies* (PATH, 2009).

The PATH *Procurement Capacity Toolkit*, Module 6, identifies six major challenges that must be taken into consideration when preparing Bidding Documents:

- finding or developing a model Bidding Document that is appropriate for this specific purchase;
- reaching decisions on details that must be included in the Bidding Documents;
- thinking through potential problems and addressing them in the Bidding Documents;
- using clear wording and assuring consistency across different sections of the document;
- building in product quality protections;
- making sure that the purchaser's responsibility (commitment) as outlined in the Bidding Documents is what will actually happen, thus reducing the chance of bidder protest, which often leads to delayed delivery.

### 6.1 Identify information required for the Bidding Documents

The Bidding Documents should include all essential information and requirements, both technical and contractual, that the manufacturer must know in order to be able to submit a responsive bid. Some of the important information that should be provided to the manufacturer includes:

- instructions, rules, and procedures for bidding
- where and when bids will be opened
- how bids will be evaluated and how the purchaser will select the winning bid
- any factors in addition to price that the purchaser will consider
- technical specifications and compliance requirements
- quantity, delivery schedule and delay clauses (requirements)
- national regulatory requirements
- terms and conditions for the future contract between the purchaser and the winning bidder

- request for documentary evidence of manufacturing quality assurance measures
- procedure for resolution of disputes
- shipping arrangements
- payment arrangements
- sample forms containing necessary wording for the bidder to use.

### 6.2 Decide on the prequalification procedures

***It is recommended that purchasers use only WHO/UNFPA prequalified manufacturing sites.*** The purchaser decides on the pre-qualification procedures that will be used for procurement. If, however, the purchaser does not choose to use only WHO/UNFPA prequalified TCu380A IUD suppliers, it is recommended that a prequalification process be conducted in accordance with the procedure described in Section 2 of this document.

It is recommended that only WHO/UNFPA prequalified suppliers be included in this bidding process.

The overall objective of the WHO/UNFPA Prequalification Scheme is to prequalify manufacturers of TCu380A IUDs of assured quality, at specific manufacturing sites, for procurement by United Nations agencies and other bulk procurement agencies.

Specific objectives of the WHO/UNFPA Prequalification Scheme are to:

- promote the procurement of TCu380A IUDs from manufacturing sites that have been assessed as having the capacity to produce good-quality products;
- establish a system that promotes the procurement of TCu380A IUDs that conform to the international standard *ISO 13485*<sup>8</sup> and the

<sup>8</sup> ISO documents are available from: International Organization for Standardization, ISO Secretariat, 1, ch. de la Voie-Creuse, CP 56, 1211 Geneva 20, Switzerland (<http://www.iso.org>).

*WHO/UNFPA TCU380A IUD Specification* as described in this document and that retain their effectiveness throughout their stated shelf-life;

- broaden the supplier base for TCU380A IUDs that are deemed acceptable, in principle, for procurement by United Nations agencies and other bulk procurement agencies;
- maintain and publish a list of prequalified suppliers.

### **6.3 Verify suppliers' manufacturing capacity**

The Bidding Documents should include a request to suppliers to provide the following documentary information:

- evidence that they are a primary manufacturer (i.e. one that undertakes the processes of moulding, assembly, sterilization and packaging, as specified by UNFPA in the call for an EOI, referred to below. One or more of these processes may be carried out on a contract basis, but the manufacturer retains overall responsibility for product quality);
- production history and products currently manufactured;
- at least two references with postal and e-mail addresses and telefax and telephone numbers;
- production capacity of the factory, available production capacity for this order and standard LOT size;
- regulatory compliance credentials and applicable national regulatory code;
- other quality management certifications;
- data to support compliance with the general and performance requirements specified in the *WHO/UNFPA TCU380A IUD Specification*;
- statement of the ability to comply with the specification attached (this statement may be incorporated into the bid form);
- explanation of the manufacturer's codes and markings.

### **6.4 Seek information about potential suppliers**

The purchaser should request information on the potential supplier's financial situation, years in business and list of key clients. This will establish that there is adequate working capital available to ensure the timely supply of raw materials and that all necessary factory maintenance can be carried out. The purchaser should always request references from the potential supplier so that the purchasing entity can contact the references and request feedback on the supplier's performance and reputation.

### **6.5 Prepare the Bidding Document package**

The information and documents discussed above are assembled into a Bidding Document package. The names of Bidding Document sections and their precise contents will vary depending upon donor, national and purchasing entity requirements, but the following list represents the essence of a good public-sector Bidding Document:

- general instructions to bidders
- special instructions to bidders
- eligible/ineligible countries and suppliers
- general terms and conditions of the contract
- special terms and conditions of the contract
- procedure for the resolution of disputes
- technical specifications
- schedule of requirements and delivery dates
- evaluation criteria
- qualification criteria
- bid and contract forms, which include:
  - price schedule
  - bid security form
  - performance security form
  - contract agreement form.

Many organizations, funders, and government entities wish to review and approve draft Bidding Documents before they are made available to the public. Changes or corrections may be required as a result of this review. Changes should be undertaken with great care, as it is easy to forget to make corresponding changes in other sections of the documentation.

For more information on preparing Bidding Documents and the details and specific information that is found under each of the above Bidding Document package headings, see Module 6 of PATH's *Procurement Capacity Toolkit*.

### 6.6 Invite bids

When the documents are ready for issue, the procuring entity can begin soliciting bids by extending a public invitation to bid to all interested firms and parties. Alternatively, they may restrict the bids to the WHO/UNFPA list of prequalified suppliers.

### 6.7 Receive and manage bids

Basic rules for receiving and managing bids:

- Bids must be held unopened in a secure location until the stated day and time of bid opening.
- Bid envelopes should be stamped with the date and time that they are received.
- *No one associated with the procurement is permitted to communicate with bidders from the time the advertisement appears until after an award has been made, except for written communication directly related to clarifying minor deviations from the information requested in the bid.*
- Procedures must be in place and adhered to for opening and reviewing the bids.

## 7 Step 7: Select suppliers<sup>9</sup>

Potential suppliers will submit Bidding Documents in response to the advertised invitation to bid. The purchasing entity convenes a committee and opens the bids at the time designated in the Bidding Documents and then begins the evaluation process to determine which supplier should be awarded the contract.

The committee evaluating the suppliers' Bidding Documents should include procurement specialists and also TCu380A IUD quality experts with the technical expertise to help evaluate the documentation and certification submitted by suppliers. The evaluation

<sup>9</sup> For more information on evaluating bids and selecting suppliers, see Module 7 of the *Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies* (PATH, 2009).

The supplier is chosen on the basis of:

- WHO/UNFPA prequalified supplier
- quality of the product
- capacity to supply
- price
- ability to meet the requirements of the contract.

It is important to consider all five factors.

**Selection should not be based on price alone.**

Select the most economically advantageous bid that meets the selection criteria.

committee also should check to see that the suppliers have confirmed that:

- they are capable of providing the quantities required within the desired time frame;
- they have a proven record of manufacturing products that conform to the *WHO/UNFPA Specification*, the purchaser's specification, or similar requirements;
- they are WHO/UNFPA prequalified suppliers, if that qualification has been identified in the Bidding Documents as a requirement for bidding;
- they will permit a sampling agency to perform random sampling of TCu380A IUDs at the manufacturing facility;
- they will accept the test results of an independent laboratory agreed to by both parties;
- they will accept the procedure for the resolution of disputes;
- they will accept the general and specific conditions of the contract.

Any supplier that has not submitted the required documentation and certification, has not adequately responded to the requests of the bidding package, or is found for other reasons to be non-responsive by the

evaluation committee is removed from consideration for the contract award.

Non-specialized procurement agents and importers should be eliminated from the list of potential suppliers.

The supplier should be chosen based on:

- being listed as a WHO/UNFPA prequalified supplier, if that qualification has been identified in the Bidding Document
- proven supplier of quality products
- demonstrated capacity to supply
- price
- ability to meet the requirements of the contract.

Suppliers should not be selected based on price alone.

Once the committee has identified and qualified the winning bidder, the committee makes a recommendation to the contracting authority for contract award. Upon approval or endorsement of the recommendation by the contracting authority, a contract can be awarded to the winning supplier.

### 8 Step 8: Contract negotiation/award

After the supplier has been selected and the contracting authority has approved the supplier recommendation, the contract needs to be prepared, signed and awarded. Often, there is a time limit for obtaining contract signatures. This step also includes deciding on payment methods.

The first responsibility for contract execution lies with the purchaser, who provides some type of payment guarantee to the supplier. Particularly in trade with developing countries, manufacturers usually do not enter an order into production until this payment guarantee is in place.

Manufacturers frequently have a backlog of orders for products in high demand, and so quickly establishing the payment guarantee keeps the delivery date on track. The most prevalent payment guarantee is a commercial letter of credit (L/C) opened at a reputable international bank by the purchaser in favour of the seller. The purchaser deposits money in the bank to “collateralize” the L/C; the bank then holds it until the seller provides documentary evidence that it has complied with its terms and conditions. The payment guarantee completes the series of events required to secure performance commitment of both the purchaser and the supplier and begins the performance stage of the supply process.

## Phase 3: Performance

### 9 Step 9: Contract performance and monitoring<sup>10</sup>

Once both parties sign a contract and payment arrangements are in place, the purchaser is responsible for monitoring the supplier’s performance of its contract obligations.

Proactive contract management and performance monitoring that engage the supplier’s support allow the purchaser to obtain information on any supplier production and performance problems at an early stage in their development. Early identification improves the chances of resolving a problem before it significantly affects the product delivery schedule. It can also be more cost-effective, since early problem identification allows the purchaser and supplier to consider a broader range of options, thereby minimizing the need to resort to more costly solutions such as delaying shipments.

***UNFPA will periodically monitor the quality of the products produced, and these reports, if available, can be requested.***

The shipping agent and manufacturer should ensure that all required documentation for the shipment is forwarded to the appropriate national authority as specified in the contract.

<sup>10</sup> For additional information refer to Modules 8 and 9 of the *Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies* (PATH, 2009).



If there are any problems or doubts about the quality of the product, follow the procedure detailed in Section 1, Chapter 4, Resolution of Disputes.

### 10 Step 10: Delivery of goods<sup>11</sup>

Public-sector contraceptives are normally shipped via ocean unless the supply source is close enough for trucking. Both of these options are far less expensive than air, which is usually reserved for emergency situations.

The contract between the supplier and the client will include a clear statement, known as an INCOTERM, that defines when the ownership, responsibility and liability for a shipment is transferred from the supplier to the client and/or receiving country.

#### 10.1 Customs clearance

It is advisable to know the procedures for customs clearance before a contract is awarded to the supplier. The purchase contract should identify all customs documentation that the supplier needs to provide for the shipment to clear customs. Being well prepared can reduce the time that the TCu380A IUDs are left sitting on the dock, which not only incurs demurrage (storage) charges but also can damage the TCu380A IUDs if they are not stored properly.

At the port of entry the regulatory licensing status of imported goods, including contraceptives and pharmaceuticals, is appraised. The purchasing entity may hire a customs clearing agent to complete the necessary paperwork and obtain a release from customs. When this is not accomplished within a few days, the port authority applies demurrage charges, which can add up to significant sums of money.

Upon release from customs, it is up to the purchasing entity to transport the goods to its own warehouse. Some customs clearing agents will make this arrangement, and sometimes a local representative of the

supplier will do it. In most cases, however, the purchaser sends its own trucks or hires private transport.

Once the TCu380A IUDs are delivered to the initial warehouse, personnel perform a receiving inspection, confirming that all goods are present according to the accompanying packing slips, are in good condition, and that product names and Latest Insertion Dates are clearly marked.

If the products pass receiving inspection, they are accepted; inventory records are updated to reflect receipt; and the product is officially placed in warehouse storage for distribution to and use by the programme.

If the product does not pass receiving inspection, a receiving report documenting the discrepancy is prepared and submitted to the purchasing entity, who has responsibility for following up with the supplier to establish the cause of the discrepancy. If appropriate, recourse can then be obtained in accordance with the conditions of the contract.

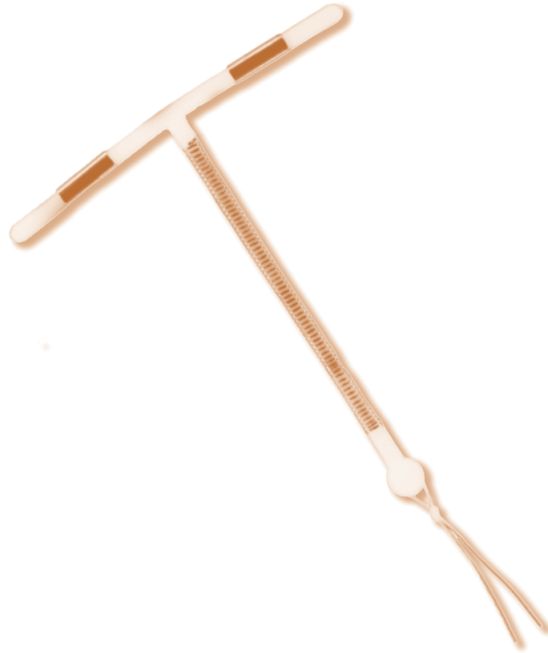
#### 10.2 Confirmatory testing

Some national regulatory authorities may insist on undertaking confirmatory testing upon receipt of the shipment to ensure that the TCu380A IUDs have not been damaged during shipping. These requirements should be written into the contractual agreement between the purchaser and the receiving country and/or procuring agency. The testing should be undertaken by a laboratory accredited to *ISO 17025*.

Confirmatory testing should be restricted to LOTS selected at random from a full shipment or consignment. It is recommended that priority be given to critical performance parameters—package integrity; dimensional, strength, and flexibility parameters; and critical workmanship compliance.

The risk of statistical LOT failures due to sampling error should be considered when interpreting the results of such tests. If there are any problems or doubts about the quality of the product, then the procedure detailed in Section 1, Chapter 4, Resolution of Disputes, should be followed.

<sup>11</sup> For additional information see Module 10 of the *Procurement capacity toolkit: tools and resources for procurement of reproductive health supplies*. (PATH, 2009).



## **CHAPTER 8**

# **Specification and Procurement Checklists**





## SECTION THREE

### CHAPTER 8: SPECIFICATION AND PROCUREMENT CHECKLISTS

#### 1 Introduction

These checklists are designed as useful tools to ensure that every step in the preparation of a specification and in the procurement process has been effectively addressed. They can be photocopied and/or downloaded from the following web sites: UNFPA: <http://www.unfpa.org/public/procurement>; WHO: <http://www.who.int/rhem/prequalification/9789241500999/en/index.html>; and RHR: [http://www.who.int/reproductivehealth/publications/family\\_planning/9789241500999](http://www.who.int/reproductivehealth/publications/family_planning/9789241500999). They can also be adapted for use with other contraceptives.

#### 2 Specification Checklist

Refer to Section 1, Chapter 2. Check the cycle of procurement, as it can take between 12 and 18 months to procure TCu380A IUDs and other contraceptive supplies. The checklist is a reminder of all the information that needs to be collected and tasks that need to be undertaken before and during the procurement process. The action column is there to either summarize the action taken or act as a reminder of action that must be taken. The comments column is for follow-up notes.

WHO/UNFPA Specification Checklist			
Step	Checklist	Action	Comments/notes
1	Are the TCu380A IUDs for: <input type="checkbox"/> Social marketing programmes <input type="checkbox"/> Public sector <input type="checkbox"/> Both		
2	Target population		
3	What are the regulatory requirements? (Refer to Procurement Checklist)		
	What are the customs clearance requirements? <input type="checkbox"/> Clearance <input type="checkbox"/> Exemptions/waivers <input type="checkbox"/> Documentation required		
	What are the programmatic requirements?		
4	Where are stocks of TCu380A IUDs held?		
	How long will existing stocks last?		
	What is the delivery schedule?		
	What quantity is needed over what period of time?		
	What is the storage capacity—where and what quantity?		
	Is a distribution system in place?		
5	Are prequalified suppliers reviewed?		
6	Is the specification reviewed and finalized?		
7	Specify packaging		

WHO/UNFPA Specification Checklist			
Step	Checklist	Action	Comments/notes
8	<p>Are packaging requirements checked?</p> <p><input type="checkbox"/> Inner boxes and outer cartons according to <i>WHO/UNFPA Specification</i></p> <p><input type="checkbox"/> Markings of inner boxes and cartons according to WHO/UNFPA Specification</p> <p><input type="checkbox"/> Inner pack quantity</p> <p>Any additional requirements:</p> <p><input type="checkbox"/> Logo?</p> <p><input type="checkbox"/> Address of procuring agency?</p> <p><input type="checkbox"/> Donor logo?</p>		

### 3 Procurement Checklist

Check the cycle of procurement, as it can take between 12 and 18 months to procure TCu380A IUDs.

Procurement Checklist			
Step and checklist	Yes	Date completed	Comments/notes
<b>Step 1: Define supply requirements</b>			
<i>1.1 Define programme context</i>			
Which donor agencies, nongovernmental agencies, social marketing agencies, commercial enterprises and different public-sector ministries are involved in the procurement, distribution and promotion of TCu380A IUDs?			
What are the sources of funding?			
What sources of supply are used?			
History of TCu380A IUD procurement over the last three years			
<i>1.2 Forecast programme requirements</i>			
Research population's current needs and unmet needs			
History of previous shipments			
Trends in TCu380A IUD use and procurement			
What is the desired buffer stock level?			
Is there a Logistics Management Information System in place that captures stock level and distribution?			
What are the requirements of National Regulatory Authorities regarding procurement, importation and confirmatory testing?			
How are TCu380A IUDs imported into the country?			
Problems encountered in past procurement of TCu380A IUDs			
Length of previous procurement cycles			
Current stock levels and where TCu380A IUDs are stored What is the annual consumption? How many months will current supplies last? Any products that may not be distributed before latest expiry date?			
Projected time-scale for distribution			
Projected requirements			
Time-scale for delivery			
Storage and distribution systems in place			

Procurement Checklist			
Step and checklist	Yes	Date completed	Comments/notes
<b>Step 2: Customize the specification</b>			
Refer to <i>WHO/UNFPA TCu380A IUD Specification</i>			
Other issues			
<b>Step 3: Assess procurement options</b>			
Select one method: i) Procure directly from a manufacturer through competitive bidding process ii) Source from a procurement agency iii) Source from an international procurement agency/ organization iv) Buy from a social marketing organization			
<b>Step 4: Budget, funding and procurement requisition</b>			
Procurement costs estimated to determine budget: <ul style="list-style-type: none"> <li>• Unit price</li> <li>• Freight cost and insurance</li> <li>• Sampling and testing</li> <li>• Import/customs clearance costs</li> <li>• Post-shipment confirmatory testing</li> <li>• Taxes</li> </ul>			
Also consider: <ul style="list-style-type: none"> <li>• Warehouse and storage costs</li> <li>• Distribution costs</li> <li>• Promotion costs</li> </ul>			
Funding identified and secured			
Identify key challenges and how you will deal with them			
<b>Step 5: Procurement planning</b>			
Obtain authorization to contract and commit funds			
Confirm budget allocations and timing for availability of funds			
Review technical specifications to ensure that they are complete and in a format consistent with international standards			
Confirm the date of delivery, location and mode of transport			
Visit customs authorities and discuss procedures			
Review regulations covering national regulatory procedures, importation and distribution of TCu380A IUDs			

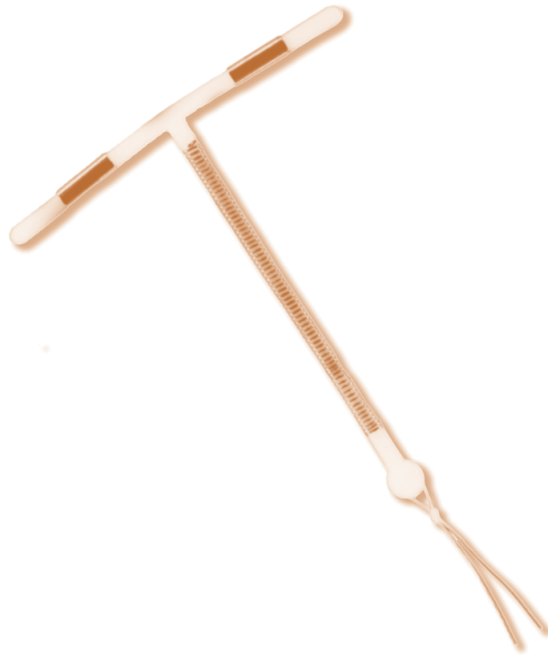
Procurement Checklist			
Step and checklist	Yes	Date completed	Comments/notes
Confirm specific country requirements and national regulatory procedures: <ul style="list-style-type: none"> <li>• Is there a mandatory national quality standard?</li> <li>• How are the standards applied?</li> <li>• What entry requirements are there?</li> <li>• Is there a registration requirement prior to importation?</li> <li>• Is confirmatory testing required?</li> </ul>			
Visit National Regulatory Authority and review and understand procedures			
<b>Step 6: Developing Bidding Documents and inviting offers</b>			
Information required for Bidding Documents identified: <ul style="list-style-type: none"> <li>• Instructions, rules, and procedures for bidding</li> <li>• Information about where and when bids will be opened</li> <li>• Information about how bids will be evaluated and how the purchaser will select the winning bid</li> <li>• Information about any factors in addition to price that the purchaser will consider</li> <li>• Technical specifications and compliance requirements</li> <li>• Quantity, delivery schedule and delay clauses (requirements)</li> <li>• National regulatory requirements</li> <li>• Terms and conditions for the future contract between the purchaser and the winning bidder</li> <li>• Request for documentary evidence of manufacturing quality assurance measures</li> <li>• Procedure for resolution of disputes</li> <li>• Procedures for confirmatory testing procedures, if required by national bodies</li> <li>• Shipping arrangements</li> <li>• Payment arrangements</li> <li>• Sample forms containing necessary wording for the bidder to use</li> </ul>			
Any other issues?			
WHO/UNFPA prequalified suppliers used: <ul style="list-style-type: none"> <li>• Verify manufacturing capacity</li> <li>• Seek information on potential suppliers</li> </ul>			

Procurement Checklist			
Step and checklist	Yes	Date completed	Comments/notes
Bidding document package prepared <ul style="list-style-type: none"> <li>• General instructions to bidders</li> <li>• Special instructions to bidders</li> <li>• Eligible/ineligible countries and suppliers</li> <li>• General conditions of contract</li> <li>• Special conditions of contract</li> <li>• Technical specifications</li> <li>• Schedule of requirements and delivery dates</li> <li>• Evaluation criteria</li> <li>• Qualification criteria</li> <li>• Bid and contract forms, which include:               <ul style="list-style-type: none"> <li>○ price schedule</li> <li>○ bid security form</li> <li>○ performance security form</li> <li>○ contract agreement form</li> </ul> </li> </ul>			
Invitation to bid circulated: Media for advertising bid invitation known			
System for receiving and managing bids in place: <ul style="list-style-type: none"> <li>• Bid envelopes should be stamped with the date and time received</li> <li>• Bids must be held unopened until the stated day and time of bid opening</li> </ul>			
<b>Step 7: Select supplier</b>			
Is assistance required to review and interpret documentary evidence supplied by manufacturers?			
Agree on criteria for evaluating the bids			
Check to see if the suppliers have confirmed that they: <ul style="list-style-type: none"> <li>• Are capable of providing the quantities required within the desired time frame</li> <li>• Have a proven record of manufacturing products that conform to the <i>WHO/UNFPA TCu380A IUD Specification</i>, the purchaser's specification, or similar requirements</li> <li>• Are WHO/UNFPA prequalified suppliers, if that qualification has been identified in the Bidding Documents as a requirement for bidding</li> </ul>			



Procurement Checklist			
Step and checklist	Yes	Date completed	Comments/notes
<ul style="list-style-type: none"> <li>• Will permit a sampling agency to perform random sampling of TCu380A IUDs at the site of the manufacturing facility</li> <li>• Will accept, if required, confirmatory testing as previously agreed in the contract</li> <li>• Will accept the test results of an independent laboratory agreed to by both parties</li> <li>• Will accept the procedure for the resolution of disputes</li> <li>• Will accept the general and specific conditions of the contract</li> </ul>			
Eliminate non-specialized procurement agents and importers from the list of potential suppliers			
<b>Step 8: Contract negotiation and award</b>			
Choose supplier based on: <ul style="list-style-type: none"> <li>• WHO/UNFPA prequalified supplier</li> <li>• Quality of the product</li> <li>• Capacity to supply</li> <li>• Price</li> <li>• Ability to meet the requirements of the contract</li> </ul>			
Payment guarantee in place			
<b>Step 9: Contract performance and monitoring</b>			
System to proactively manage contract in place			
<b>Step 10: Delivery of goods</b>			
Are procedures for customs clearance known and implemented?			
Do you have all the appropriate information and forms required for customs clearance?			
Are regulatory requirements met?			
Is there an established procedure for the resolution of disputes?			
Do you know the delivery schedule?			
Does the regulatory authority require confirmatory testing?			
If yes, have sampling procedures and testing regime been agreed upon?			
Is the regulatory authority familiar with the process for resolving disputes?			
Has the delivery schedule been reconfirmed?			

Procurement Checklist			
Step and checklist	Yes	Date completed	Comments/notes
Has all the customs documentation been received?			
Do you need to deal with any factors that could delay receipt of the shipment?			
Are storage facilities ready and prepared to receive the shipment of TCu380A IUDs?			
Has transportation been organized?			
Are storage facilities ready and prepared to receive the shipment?			
Will they be stored on the basis of first in—first expiry out?			



## **SECTION FOUR**

### **Annexes**



## ANNEX I

### TECHNICAL BASIS PAPER: REVISION OF THE TCU380A IUD SPECIFICATION

(prepared 2007 and updated 2010<sup>1</sup>)

The purpose of this technical basis paper was to detail the issues that needed to be addressed when updating the original Population Council specification for copper-bearing 380A intrauterine devices (IUD). Details of how these issues were addressed is given in Section 1, Chapter 2.

## 1 Background

Modern copper-bearing intrauterine devices (IUDs) are a popular, safe and highly effective method of long-term, reversible contraception. The percentage of women experiencing unintended pregnancy within the first year of typical use is 0.8%, and the percentage of women continuing use at one year is 78% (1). IUDs do not interfere with sexual intercourse and, since they do not require any action on the part of the user, such as insertion immediately prior to intercourse, they are unlikely to be subject to user failure. Once inserted, they can be left in place for between 10 to 12 years, depending upon the type of IUD used. IUDs are relatively inexpensive to manufacture and widely available. It was estimated that in 2007 approximately 163 million women used IUDs, which is 23% of all users of contraceptives (2).

Plastic IUDs were first introduced to the market in the late 1950s and early 1960s (the Lippes Loop, Margulies Spiral, Saf-T-Coil, etc.). Towards the end the 1960s it was discovered that adding copper improved the effectiveness of the IUD and reduced the frequency of problems associated with bleeding. The first copper-bearing IUDs (Copper-7, TCu200, and Nova T) appeared in the early 1970s. These products required replacement every two or three years, but second-generation copper-bearing IUDs introduced towards the end of the 1970s with larger quantities of copper not only reduced the incidence of side effects but also significantly improved contraceptive efficacy rates. Among the better-known examples of these second-generation IUDs are the TCu380A, TCu220C and Multiload-375 (MLCu375).

In the mid-1980s IUDs suffered a loss of popularity when an association between the use of the Dalkon Shield, a plastic non-copper-bearing IUD, and septic abortions (i.e. abortions or threatened abortions associated with pelvic infection) was reported (3), and a case-control study in the USA (4) concluded that Dalkon Shield users were five times more likely to suffer from pelvic inflammatory disease than users of other intrauterine devices. The increase in risk associated with the Dalkon Shield has been attributed to its multifilament thread acting as a wick, allowing bacteria to enter the uterus (5) although this explanation is not universally accepted. Since that time copper-bearing IUDs have continued to be used and have proved to be highly effective and safe.

## 2 Factors affecting the safety and efficacy of copper-bearing IUDs

Copper-bearing IUDs come in a variety of shapes but usually are a T or horseshoe shape and are kept in place within the uterus by the extended arms. Frameless designs are also available; these are anchored to the wall of the uterine fundus. Copper-bearing IUDs usually consist of a plastic body around which a copper wire is wound. In some devices the copper wire has a silver core, which is claimed to delay fragmentation and increase the lifespan of the device. Initially, the copper was wound around the vertical stem only, but in more recent designs copper sleeves have been added to the horizontal arms to increase the surface area of copper (6).

A Cochrane Review (7) of the effectiveness and safety of copper-containing IUDs was published in 2006 and updated in 2007. The review was prepared by the Geneva Foundation for Medical Education and Research, the Leiden University Medical Centre, the Westminster Primary Care Trust London and the WHO Department of Reproductive Health and Research.

The purpose of the systematic review was to compare different framed copper IUDs for their effectiveness and side effects, including evidence on the possible association between IUD use and pelvic inflammatory disease. Multiple electronic databases were searched for relevant trials in all languages. A total of 748 citations

<sup>1</sup> Technical basis paper prepared and submitted by Dr William Potter, August 2007, updated 2010 and submitted for publication May 2010.

and abstracts were identified and assessed against the inclusion criteria. Only randomized, controlled studies reporting on clinical outcomes were considered. Of the citations reviewed, 87 met these criteria and were formally assessed using rigorous quality criteria. The final review analyzed 42 studies. These 42 reports comprised 34 individual trials involving nine different IUDs, resulting in 16 comparisons involving more than 50,000 women.

Of the IUDs considered in the review, the TCu380A had a lower pregnancy rate than the MLCu375, MLCu250, TCu220C and TCu200. The TCu380S, in which the position of copper on the arms has been changed relative to those of the TCu380A, did not exhibit improved efficacy. The MLCu375 was no more effective in preventing pregnancy than the TCu220C at one year, the MLCu250 at three years or the NovaT at three years. Compared with the TCu380A, none of the IUDs reviewed showed any better performance in terms of bleeding or pain or any of the other reasons for early discontinuations, except the TCu200, which had fewer removals for bleeding and pain in the first two years of use. The TCu380A was therefore preferred over the MLCu375, MLCu250, TCu220C, TCu200 and Cu-Safe 300, and indirect evidence suggested that it performs better than the NovaT and Cu7. There were no published data to support use of the NovaT380. Current devices requiring smaller inserter tubes may have an advantage for the minority of women who have a tight cervical canal. However, these devices may be associated with lower efficacy.

Following publication of the Cochrane Review, WHO/UNFPA convened an IUD Technical Review Committee Meeting to consider the findings of the review and the implications for public health. International experts and researchers in the field of IUDs together with the convenor of ISO/TC 157 WG3 (the international standards committee responsible for developing the international standard for copper-bearing IUDs (*ISO 7439*)), and other representatives of ISO/TC 157 (the international standards committee responsible for mechanical contraceptives, the authors of the Cochrane Review and representatives from WHO Secretariat) attended the meeting, which was held on 19–20 September 2007 in Geneva.

After considering the Cochrane Review, the IUD Technical Review Committee reached the following conclusions:

- For a given IUD design there is a trend towards greater efficacy with increased nominal surface area of copper on framed devices.
- The evidence indicates that in general copper on the arms of an IUD improves IUD efficacy.
- Only one comparison allowed consideration of the frame design per se. In this comparison, MLCu250 versus NovaT200, there was no difference in efficacy.
- Surface area and placement of copper on framed devices appears to be more important than the shape of the device.
- There is insufficient evidence to address whether a shorter vertical stem offers any advantage in nulliparous women.
- The Cochrane Review did not include information on the insertion device. Further investigations are required to measure the insertion device against the specifications set by the original manufacturer.
- There was no evidence in the Cochrane Review that the relative performance of different framed copper IUDs varies between age groups.
- There is no evidence that any particular framed copper device is better suited to nulliparous women.
- No framed copper device showed consistently lower removal rates for bleeding and pain than other framed copper devices.
- Other than the Cu7, expulsion rates of framed devices reviewed did not appear to depend on the design of the device or copper loading.
- In the trials reviewed, there was no evidence that any one framed copper device is associated with a greater risk of ectopic pregnancy than others. However, data from other studies indicated that higher copper load devices showed a lower risk of ectopic pregnancy.

- There was no evidence that any one framed copper device was associated with a greater risk of discontinuation for pelvic inflammatory disease (PID). (Note: The diagnosis of PID is rarely standardized between studies.)

Also, the Technical Review Committee agreed to make the following recommendations to ISO/TC 157 WG3 to be taken into consideration in the international standard for copper-bearing IUDs (*ISO 7439*):

- Clinical performance criteria should be those that can be measured objectively. These include pregnancy and expulsion rates, as stated in *ISO 7439*, Section 4.2.
- Overall discontinuation rates are important indicators of performance that should be considered.
- The requirement on expulsion rates should be modified to state that: “The combined partial and complete expulsion rates should be less than 10/100 during the first year as calculated by life-table analysis”.
- Based on the evidence reviewed, both the point estimates and the upper 95% confidence intervals of the one-year pregnancy rates for two devices, the TCu200 and Cu7 (no longer available), were reported to have exceeded 2.0 per 100 women.
- Eliminate use of the Pearl Index and adopt only single decrement life-table analysis.
- No framed copper IUDs in this review exceeded the requirement on expulsion rates.

Specifically, an IUD for public distribution shall meet the following clinical performance requirements:

- The upper limit of the two-sided 95% confidence interval for the one-year pregnancy rate computed using life-table methods shall be less than or equal to 2%.
- One-year expulsion rates computed using life-table methods shall be less than or equal to 10%.

- One-year discontinuation rates computed using life-table methods shall be less than or equal to 35%.

A number of other recommendations to ISO/TC157 WG3 concerning the revision of the international standard *ISO 7439* were also agreed. These are appended (Annex IV). The Technical Review Committee agreed that a revised specification for the TCu380A device should be developed.

### 3 The TCu380A IUD

The TCu380A IUD was developed jointly by the Population Council and the FEI (FEI Women’s Health LLC and FEI Products LLC) (8). The Population Council is an international non-profit, nongovernmental organization that seeks to improve well-being and reproductive health. FEI is a women’s health care company specializing in the manufacture and marketing of intrauterine contraception. The first IUD developed by the Population Council in 1967 was made from plastic in the shape of a T. This was followed by the Copper T 200 (TCu200), the first of the copper T family of IUDs. Further development led to the TCu380, which has copper collars on the horizontal arms and copper wire coiled around the vertical stem, and then to the TCu380A. The United States Food and Drug Administration (USFDA) approved the TCu380A for marketing in 1984.

The TCu380A IUD is made of polyethylene with barium sulphate added for X-ray opacity. It has a solid copper sleeve on each of its two transverse arms, each of which has a surface area of 35 mm<sup>2</sup>, and copper wire of 310 mm<sup>2</sup> surface area wound tightly around the vertical stem. The device is 32 mm wide and 36 mm long, with a plastic ball at the bottom of the vertical stem to guard against cervical penetration. A clear or colourless polyethylene filament is tied in a knot through the ball to provide two marker threads.

### 4 Population Council specification

The Population Council specification for the TCu380A IUD specifies the materials, dimensions and properties of the device. The specification was submitted to the USFDA in NDA 18–680 (Copper T

Model TCu380A) and forms the basis of the approval for the product. The specification requirements are summarized in Annex II.

## 5 Frame

The frame is made from low-density polyethylene (LDPE). The Population Council specify DuPont 20, a specialty low-density polyethylene resin with a low melt index and intermediate crystallinity. The manufacturer states that the polymer is produced by a unique polymerization process and that it has outstanding flexibility and environmental stress crack resistance. It was also claimed to be a “clean” grade suitable for medical use. Other requirements of the Population Council specification for the polymer are: density 0.906 to 0.929 (units not specified); identification by infrared spectrum (the spectrum included in the specification is in fact for Alathon 2005); and that the material passes US Pharmacopeia (USP) class II extraction limits for plastics.

Typical values for the physical properties of DuPont 20 as published by the manufacturer are given in Table 1.

In a separate summary table the Population Council specifies that the LDPE should comply with *ASTM*

*D1248* Type 1, Class A, Category 3. The standard referred to is undated, but it is probably an earlier version of the current standard, *ASTM D1248–05* (the table itself is also undated). *ASTM D1248–05* covers polyethylene extrusion plastic materials for wire and cable. Type 1 signifies that the density should be in the range of 0.910 to 0.925 g/cm<sup>3</sup>; Class A signifies that the polymer should be natural in colour; and Category 3 signifies that the melt flow index should be in the range > 1.0 to 10 gram per 10 minutes at 190 °C with a 2.16 kg load. The “grade”, which in *ASTM D1248* determines the specification limits for physical properties including tensile strength, elongation at break, resistance to environmental stress cracking and brittleness temperature, is not specified. There is clearly a small inconsistency between the density range specified in *ASTM D1248–05* for Type 1 polyethylene (0.910 to 0.925 g/cm<sup>3</sup>) and the range quoted by the Population Council (0.906 to 0.929).

In order to make the device opaque to X-rays and so facilitate detection within the body, the Population Council specifies that the moulding powder for the frame shall contain between 20% and 24% barium sulphate. USP grade barium sulphate from Picker Corporation Nuclear Department is specified. The amount of barium sulphate is determined by a standard USP method (ash determination).

**Table 1. Typical values for the physical properties of DuPont 20**

Property	Nominal value	Test method
Density	0.92 g/cm <sup>3</sup>	ASTM D792— ISO 1183
Melt index	1.9 g/10 min (190 °C/2.16 kg)	ASTM D1238— ISO 1133
Melting point	108 °C (226 °F)	ASTM D3418— ISO 3146
Vicat softening point	94 °C (201 °F)	ASTM D1525— ISO 306
Freezing point	92 °C (198 °F)	ASTM D3418
Flexural modulus	157 MPa (22,771 psi)	ASTM D790
Tensile elongation at break	600%	ASTM D638— ISO 527–2
Tensile strength at break	16.1 MPa (2335 psi)	ASTM D638— ISO 527–2
Durometer hardness (Shore D)	49	ASTM D2240— ISO 868

There is a requirement that frames made from each new LOT of moulding powder should be tested for tissue reactions by intramuscular implantation in two rabbits for at least 72 hours. Animal testing on a routine production basis of this nature is still used in certain cases, for example the rabbit pyrogen test for determining endotoxin levels for injectables and certain implants, but by and large they are now being replaced by *in vitro* methods. By adequately specifying the materials, it should be possible to eliminate this requirement from the specification, except for qualification purposes if different grades or materials or perhaps materials from different manufacturers are used.

Frame dimensions are specified. A test and requirement for frame flexibility was specified in the original Population Council specification. However, inadequate details were given about the



equipment and test method. Following discussions with manufacturers, an improved description of the test method has been included in the *WHO/UNFPA Specification* along with a photograph of an example of the test equipment used.

The methodology of this test was reviewed and, after clarification, has been retained.

There is no strength requirement relating to the attachment of the arms to the frame. The amount of recovery achieved (memory) when the arms are folded to a specified angle for 5 minutes is also unspecified.

There was no discussion in the Population Council specification relating to moulding defects such as moulding flash, etc., nor were there any limits set for obvious visual defects. These have now been added to the specification.

## 6 Copper

In the Population Council specification the copper wire is referred to as Grade 1 PDOF level of impurities (99.99% pure). It is not clear which standard or specification the “Grade 1” refers to, but it is probably *ASTM B170–99* (2004). It is also not clear what the designation PDOF means, but it is probably Phelps-Dodge Oxygen Free (Phelps Dodge Mining is a major copper producer). Grade 1 copper is also designated C10100 according to the unified numbering system (UNS) developed by the United States National Bureau of Standards and has a purity of at least 99.99% (9). It is the highest purity oxygen-free electronic (OFE) copper. Equivalent grades are C1011 in Japan; C110 in Britain; Cu-c2 in France; Cu-OFE in many other parts of Europe including Switzerland, Britain, Italy, the Netherlands, Portugal and Hungary; Cu 99.97B in Poland; M00b in Russia; and OFE in Australia. Some care has to be exercised when looking at designations according to different standards and countries. For example, the British designation C101 is equivalent to UNS C11000 and not to UNS C10100.

The oxygen content of the copper was not specifically stated in the Population Council Specification, but a maximum limit of 0.0005% is specified for C10100

and equivalent grades. This limit for oxygen content was therefore added to the specification for copper (see Annex III). The most commonly used grade of copper for electrical wiring is UNS C11000 (also known as Electrolytic Tough Pitch, or ETP), which is 99.90% pure. It is unlikely therefore that ordinary off-the-shelf copper wire will meet the purity requirements specified. Limits on specific impurities are listed in the specification (see Annex III). Assuming that a copper of purity 99.99% is required, then it is necessary to specify UNS C10100 copper or equivalent.

The copper tube used for the collars is specified as OFHC half hard temper 99.99% pure. OFHC stands for oxygen-free high conductivity, but this acronym has now been replaced by OFE. Essentially, therefore, the copper tube is of the same UNS C10100 grade as the wire. The specifications for impurities for the tubing and the wire are identical (see Annex III).

The dimensions of the wire and tubing are specified fully, but there are no requirements for physical properties such as tensile strength, etc.

## 7 Thread

A length of thread (thread or suture) is attached to the base of the device to facilitate removal. In the Population Council specification a high-density grade of polyethylene, Philips Marlex 6006, with a density in the range 0.959 to 0.969, is specified, whereas in a separate summary table high-density linear polyethylene (*ASTM D1248* Type IV, Class A, Category 4 or equivalent) is specified. Again, the standard is undated. Inspection of *ASTM D1248–05* indicates that this specifies a natural colour with a density greater than 0.96 g/cm<sup>3</sup> and a melt flow index in the range > 0.4 to 1.0 g/10 minutes (190 °C, 2.16 kg load). Again, the “type” is not specified, hence neither are the physical properties of the thread.

The specification states that the thread can contain up to 1% titanium dioxide (no lower limit is specified), whereas the separate summary table specifies 2% to 4% titanium dioxide. A supplier for the thread is specified (Albany International, Canada). Dimensions (thickness and length) are specified (see Annex II), and

there is a strength test to ensure that the thread and/or thread attachment meet a specified minimum.

The original specification states that an intramuscular implantation test in rabbits should be conducted on each LOT of thread. This again raises the issues discussed earlier concerning the frame.

## 8 Insertion instrument

The insertion instrument comes in three parts, according to the Population Council specification: a solid rod of polypropylene (with 0.5% titanium dioxide added as a colorant), an insertion tube made from polyethylene (density 0.959 to 0.969 according to *ASTM D1505–85*) and a flange made from PVC containing titanium dioxide and FDC Blue #1. There are no requirements relating to the specific grades of these materials, nor to the amount of titanium dioxide and blue pigment added to the flange in the main specification. The summary table specifies the same *ASTM D1248* requirements for the polyethylene tube as for the thread and adds “medical grade” for the PVC. Dimensions are specified adequately for the rod, insertion tube and the diameter of the hole on the flange, but there is no requirement for the shape and outer size of the flange. There are no requirements covering the physical properties of the insertion device other than the force required to displace the flange, which should be in the range 0.46 lb to 2.0 lb. Failures below the 0.46 lb limit are classified as major defects, whereas those over the upper limit of 2.0 lb are classified as minor defects.

## 9 Packaging

The packaging specified in the original specification is clearly intended for ethylene oxide sterilization and as such has to be permeable to gas and moisture but still function as a microbial barrier. A laminated polyethylene and Mylar polyester film (Tower 1411 or 1440) is specified for one side and Tyvek 1073B (American Converters/Tower of Mundelein or Rexham Health Care Packaging) for the other side. The thicknesses of the polyethylene and Tyvek are specified, but it is not clear if the original specification refers to the polyethylene component alone or the total laminate thickness.

For a sterile medical device, such as an IUD, it is critical that pack integrity and pack seal strength are adequate. The Population Council specification requires visual inspection of the pack seal during manufacture and a pressure test using proprietary equipment (ARO automatic Test-A-Pack System) on a minimum sample of 32 packs taken from each LOT (or 1 per 800 finished units). The sampling scheme is effectively a double sampling plan (2x32) with not more than one pack out of the combined sample of 64 exhibiting a seal rupture when 33 inches of water pressure is applied for a period of 30 seconds. This is equivalent to an AQL of 1.0 (*ISO 2859–1*). The Population Council specification states that this test is equivalent to a peel strength test with a minimum tensile strength requirement of one pound per one-inch strip.

Specifications for the packaging of sterile medical devices are covered by the recently published international standards *ISO 11607* Parts 1 and 2 (*Packaging for Terminally Sterilized Medical Devices*). Part 1, *ISO 11607–1:2006*, covers requirements for materials for sterile barrier systems and packaging systems, while Part 2, *ISO 11607–2:2006*, covers validation requirements for forming, sealing and assembly processes. These new standards harmonize previous ISO and European requirements. The intent of these standards is to ensure that the integrity of the final package is maintained at least for the claimed shelf-life of the medical device under the storage conditions specified by the manufacturer. In reviewing the IUD specification, note should be made of any relevant requirements relating to packaging described in these standards.

## 10 Sterilization

The Population Council specification specifies sterilization by ethylene oxide using terminal testing of *Bacillus subtilis* spore strips to monitor the process (biological indicator). Limits and testing methods for ethylene oxide residues (ethylene oxide, ethylene chlorohydrin and ethylene glycol) are specified. There are no requirements relating to bioburden levels prior to sterilization nor are there any requirements to validate the process.

Until very recently ethylene oxide sterilization was covered by two separate standards, *ISO 11135:1994*, adopted by ANSI/AMMI in the United States, and *EN 550* in Europe. These standards have recently been harmonized, and a new ISO standard, *ISO 11135-1:2007 Sterilization of Health Care Products—Ethylene Oxide. Part 1. Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices*, has just been published.

Various methods are specified for validating ethylene oxide sterilization. One of the most common is the overkill method, although parametric-release is becoming widely used. Before validation the required sterility assurance level (SAL) should be defined, taking into account the device's intended use. The SAL is the probability of a single viable micro-organism occurring on an item after sterilization. Its value may vary between  $10^{-3}$  for topical devices and  $10^{-6}$  for blood-contact invasive devices. The commonly accepted SAL for invasive medical devices is  $10^{-6}$ , and some European countries will accept only this value.

Release of ethylene oxide sterilized product is typically controlled using a biological indicator as per the Population Council specification, although routine bioburden monitoring is also recommended to verify control of the manufacturing process. Alternatively, parametric release of product following a successful validation and conformance to the processing parameters established during validation may be used. Parametric release does not require a biological indicator.

Finally, ethylene oxide residuals in medical products are specified in *ISO 10993-7:1995/(R)2001*. Confirmation that the residual ethylene oxide limits specified by the Population Council comply with the requirements of this standard is required.

Consideration also needs to be given to the possibility of approving radiation sterilization for the TCu380A. Radiation sterilization may offer advantages in terms of cost-effectiveness, higher levels of sterility assurance and faster turnaround times. Using radiation sterilization would also allow a wider range of packaging to be used, particularly continuous film packs which may provide more protection against copper tarnishing. The use of gamma radiation for sterilizing TCu380A IUDs is

very widely practiced, even though this falls outside the Population Council specification.

Radiation sterilization can impact negatively on the properties of plastic materials, leading to discolouration, loss of strength, and embrittlement. Low-, medium- and high-density polyethylene have good-to-excellent radiation resistance and can tolerate doses of up to 500 kGy (compared with typical sterilization doses of 25 kGy) (10), but such high doses may adversely affect the ageing properties of the material. The main components of the IUD are therefore unlikely to be adversely affected initially by radiation sterilization, although ageing properties might be compromised. WHO commissioned a study to assess the long-term service life of the product. This study did not identify any evidence of oxidative degradation occurring *in utero*. Based on this study, it is considered unlikely that radiation sterilization has any adverse effect on the service life of the product (see Annex VI).

Polypropylene has poor radiation resistance, with a maximum dose tolerance of less than 50 kGy. The insertion rod, which is made from polypropylene, may therefore be adversely affected and as a consequence the shelf-life of the product may be compromised. Similar comments apply to the PVC flange, although PVC is more resistant than polypropylene and should be able to tolerate a dose of 50 kGy.

Sterilization by radiation is covered by a series of international standards, *ISO 11137-1*, *11137-2* and *11137-3*. Again, these standards have recently harmonized ANSI/AAMI/ISO and European requirements (*EN 552*).<sup>2</sup>

The topics covered by these three standards are:

*ISO 11137-1* specifies requirements for the development, validation and routine control of a radiation sterilization process for medical devices.

*ISO 11137-2* specifies methods of determining the minimum dose needed to achieve a specified requirement for sterility and methods to substantiate

<sup>2</sup> Note: All references to ISO standards refer to the latest published edition of that standard, except when a year is specified.

the use of 25 kGy or 15 kGy as the sterilization dose to achieve a SAL of 10<sup>-6</sup>. It also specifies methods of dose auditing in order to demonstrate the continued effectiveness of the sterilization dose.

*ISO 11137-3* gives guidance on the requirements in *ISO 11137* Parts 1 and 2 relating to dosimetry. Dosimetry procedures are related to the development, validation and routine control of a radiation sterilization process.

Again, various methods are specified for the validation of sterilization by irradiation, all intended to confirm that a specific radiation dose is effective in achieving the required SAL for a specific product and a specified bioburden limit. Typically, validated processes are controlled by bioburden monitoring and dosimetry rather than by using biological indicators. When conducting validation programmes on medical devices, it is essential to ensure that adequate attention is given to the potential effect of the radiation on the properties and shelf-life of the product.

The following international standards also apply in general to the sterilization of medical devices:

*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 Validation of a Sterilization Process.*

*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 for Medical Devices.*

## 11 Product release testing

The Population Council specification includes the following requirements for testing the finished product prior to release:

1. The amount of wire (by weight) on the T (limits 165 to 178 mg), using a double sampling plan based on an AQL of 0.65 and an Inspection Level of S-4;

2. The diameter of the copper collars ( $0.082 \pm 0.001$  inches) and the location of the collars on the arms ( $5.4 \pm 0.4$  mm from the ends), using a double sampling plan based on an AQL of 0.65 and an Inspection Level of S-4;
3. The length of the thread (10.5 to 12.5 cm) on 50 samples;
4. The strength of the thread/IUD (2.0 lbs, equivalent to 0.907 kg, or 8.89 N) on a sample of 50 devices, with not more than one device breaking below this limit (equivalent to an AQL of 1.5);
5. Sterility using *Bacillus subtilis* spore strips containing 10<sup>6</sup> spores per strip inserted into 10 packages during sterilization and cultured for 10 days;
6. Residual ethylene oxide, ethylene chlorohydrin and ethylene glycol by head space GC on 10 samples;
7. Pouch burst strength using the ARO automatic Test-A-Pack system on 1 pack per 800 units, with a minimum pack sample size of 32.

## 12 ISO 7439 requirements

*ISO 7439* is the international standard for copper-bearing IUDs. It is a generic standard intended to cover all single-use copper-bearing IUDs. Being generic, it specifies relatively broad limits on dimensions (length not greater than 36 mm, width not greater than 32 mm) and copper content (surface area 200 to 380 mm<sup>2</sup>). Tolerances specified are  $\pm 5\%$  for dimensions and  $\pm 10\%$  for copper area. The purity of the copper is specified as 99.9% rather than the 99.99% required by the Population Council specification.

Other requirements include that the thread shall be monofilament, the device and thread shall withstand a tensile force of at least 12 N, the insertion instrument shall have a maximum diameter of 5 mm, when deformed the device shall recover to within 5 mm of its original shape within one minute, and the device shall be detectable by X-ray (if barium sulphate is used, then its content shall be from 15% to 25%).



*ISO 7439* does not specify inspection levels or acceptable quality limits (AQLs). Appropriate inspection levels and AQLs should therefore be included in any specification for the device.

In terms of product safety, *ISO 7439* requires that the device shall be evaluated in accordance with requirements of *ISO 10993-1 Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing*. The standard states that supplementary tests for chronic toxicity and carcinogenicity should be considered. *ISO 7439* also includes extensive requirements for labelling, instructions for use and information intended for women, none of which is included in the Population Council specification.

*ISO 7439* specifies that the product shall be supplied sterile but gives no guidance on sterilization methods or procedures for assuring sterility, nor does it specify a SAL. Reference is made to Clause 9, *ISO 14630 Non-active Surgical Implants—General Requirements*.

### 13 Clinical evaluation

There is a requirement in *ISO 7439:2002* for the contraceptive efficacy of a copper-bearing IUD to be determined by clinical evaluation. The evaluation should meet certain minimum requirements in terms of the total number of menstrual cycles (at least 10,000), the number of women completing (at least 400 for the first year and 200 for the third year) and the *in situ* time (three years). The requirements for pregnancy and expulsion rates are specified as in *ISO 7439:2002* are:

- “pregnancy rate  $\leq 2$  per 100 woman-years during the 1st year as calculated by life-table analysis”;
- “expulsion rate  $< 10$  per 100 woman-years during the 1st year as calculated by life-table analysis”.

Larger studies will be required to meet these requirements. Therefore, the IUD Technical Review Committee made additional recommendations to increase the size of the study to include at least 20,000 women-months for the device under test, which can be achieved by conducting a randomized study in which an average of 720 women use the test device in the

In light of feedback from the WHO/UNFPA IUD Technical Review Committee following publication of the Cochrane Review, a revision of *ISO 7439:2002* is pending that is expected to modify the clinical evaluation of these devices, as follows:

- The upper limit of the two-sided, 95% confidence interval for the one-year pregnancy rate computed using life-table methods shall be less than or equal to 2%.
- One-year expulsion rates computed using life-table methods shall be less than or equal to 10%.
- One-year discontinuation rates computed using life-table methods shall be less than or equal to 35%.

first year of the study and an average of 360 women in a control arm use the TCu380A device.

The TCu380A IUD has already undergone extensive clinical evaluation, and the IUD Technical Review Committee, based on the outcome of the Cochrane Review, concluded that not only does the device meet the current performance requirements of *ISO 7439:2002*, but it also meets proposed amendments to the standard. The review concluded that the pregnancy rate for the TCu380A IUD was in the range 0 to 1 after one year per 100 women, and the expulsion rate was in the range of 2.4 to 8.2 after one year per 100 women.

### 14 Discussion

The Population Council specification adequately specifies the TCu380A IUD in terms of base dimensions and basic physical requirements. These requirements comply with the generic requirements specified in *ISO 7439:2002*. The test methods described in the Population Council specification relate to specific types of equipment. Consideration needs to be given to extending the scope of test procedures to allow a wider choice of equipment to be used. Sample

sizes and acceptance/failure criteria are stated explicitly rather than by inspection level and AQL.

Discussions with manufacturers have highlighted a number of issues relating to the design that need to be considered. The junctions between the arms and the stem of the device are sharp right angles and as such give rise to high stress concentrations whenever the arms are deflected. On the basis of finite element analyses, one manufacturer has elected to eliminate the sharp junctions by adding a radius to reduce stress concentration and, therefore, the risk of the arms breaking off. Such a design change will not affect the efficacy of the device. It should reduce the risk of failure *in utero*, although excessively large radii could increase the stiffness of the arms and increase the risk of crush damage when the arms are bent down to load the device into the insertion tube. Manufacturers need to validate such design changes.

The specifications for the materials of construction for the device need to be updated, taking into account changes in nomenclature and specifications/standards since the Population Council specification was developed. A critical question relating to the choice of materials is whether they should be specified by manufacturer and trade name or by generic description supported by physical properties specification. In general, polyethylenes are prone to oxidation, and it is common practice to add antioxidants to these plastics to improve the shelf-life and service life of products made from them. It is perhaps surprising that antioxidant-free grades of polyethylene are specified and that no antioxidant is added, given the long shelf-life and *in utero* time associated with the TCu380A IUD. The extent to which devices from different manufacturers need to be subjected to safety and biological evaluation also needs to be reviewed. This is particularly critical if there is a move towards making the specifications for materials generic.

One manufacturer raised questions about the particle size of the barium sulphate and the quality of the dispersion obtained in the plastic. Again, this relates to the risk of detachment of the arms under stress. Excessively large barium sulphate particles or clumping of the particles may lead to excess stress

concentrations in the region where the arms join the stem of the device, leading to failure. The use of micronized barium sulphate is recommended along with a qualitative check by X-ray on the uniformity of distribution of barium sulphate within the device. The need to make the device X-ray opaque has been questioned, given the current prevalence of ultrasound scanning around the world.

The Population Council specification does not include a specification for the titanium dioxide pigment used in the thread. Additional comments from manufacturers indicate that many do not know which grade is used, but one suggests that the titanium dioxide be the rutile rather than the anatase morphology. An appropriate specification for the titanium dioxide needs to be considered. DuPont Titanium Technologies recommend a specific grade of titanium dioxide for incorporation into injection-moulded polyethylene/polypropylene, DuPont™ Ti-Pure® R-350, which has a rutile morphology. Some manufacturers and purchasers also specify that the thread should be monofilament medical-grade nylon, since this material is both stronger and produces a thread with a smoother surface than high-density polyethylene.

There is a clear discrepancy between the minimum strength of the device, as specified in *ISO 7439*, of 12 N (equivalent to 1.224 kg force) and the Population Council specification of 2.0 lbs, which is equivalent to 8.89 N (0.907 kg force). One manufacturer reported that it is difficult to meet the ISO requirement of 12 N given the specified material and thread diameter. The same manufacturer stated that it is best to retain the lower breaking force specification since it is preferable for the thread to break rather than the body of the device.

Since the Population Council specification was developed, sterilization practices have developed considerably, and it has to be considered whether the requirements and procedures described in the original specification are acceptable by modern standards. These requirements have to be reviewed against the recent harmonization of US and European sterilization practices with the publication of new ISO standards.

Requirements for sterilization validation are missing from the current specification, as are alternative methods of sterility assurance such as parametric release.

Given the prevalence of radiation sterilization among manufacturers at present, consideration has to be given to accepting this method as an alternative to ethylene oxide. When considering radiation sterilization, it is essential to be confident that adequate assessments of the effects of irradiation on the properties, shelf-life and service life of the product have been undertaken, particularly taking into account the fact that the current specifications for the materials of construction do not include antioxidants.

Similar comments apply to packaging. The current specification has to be reviewed in light of *ISO 11607* Parts 1 and 2 and modern trends in medical device packaging. A critical question is whether pack integrity and seam strength are adequately specified and assessed. Changing to radiation sterilization allows completely occlusive film-on-film packs to be used, with the advantage of extra product protection. Some manufacturers have reported that using permeable packs that do not prevent the ingress of moisture can lead to tarnishing of the copper. Film-on-film packs are also easier to test for pack integrity since various vacuum-based methods can be used.

In the consideration of the specification, it is also necessary to take into account manufacturers' current practice. It is necessary to consider the extent to which any changes in the materials, construction or even the design of the product may affect its safety, efficacy and shelf-life. What level of validation of the manufacturing process is expected? Is each manufacturer expected to undertake stability studies to guarantee that the shelf-life requirements are being met?

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## ANNEX II

### SUMMARY OF SPECIFICATION CHANGES

Summary of Specification Changes			
Attribute	Population Council	ISO 7439	WHO/UNFPA 2010
Plastic "T" frame with barium sulphate added for visibility on X-rays—material	DuPont 20 polyethylene and (20–24)% barium sulphate  Must pass extractable test for Class II plastics by method of USP (saline and saline-alcohol extracts of sample at 70 °C injected intravenously in mice)	(15–25)% barium sulphate	Low-density polyethylene (LDPE) free of stabilizers having a minimum tensile strength of 13 MPa ( <i>ASTM D638—ISO 527–2</i> ) and a 2% secant flexural modulus in the range 133.5 MPa to 180.6 MPa ( <i>ASTM D790</i> ). The LDPE shall be blended with 15% to 24% USP precipitated barium sulphate with a particle size of 95% less than 10 micron.  The compounded polymer (LDPE plus barium sulphate) shall be evaluated for biological safety in accordance with <i>ISO 10993–1:2003</i> requirements for mucosal membrane contact devices intended for permanent contact. Specifically, the following testing is required:  Testing for genotoxicity according to <i>ISO 10993–3</i>  Testing for cytotoxicity testing according to <i>ISO 10993–5</i>  Testing for irritation and delayed-type hypersensitivity according to <i>ISO 10993–10</i>  Testing for subacute and subchronic toxicity according to <i>ISO 10993–11</i>  Requirements for animal implant testing on each compounded LOT have been replaced by <i>in vitro</i> cytotoxicity testing.
Vertical stem length	(35.69–36.12) mm	36 mm maximum ± 5% tolerance (34.2–37.8 mm)	(36 ± 0.5) mm
Horizontal arms length	(31.62–32.26) mm	32 mm maximum ± 5% tolerance (30.4 ± 33.6 mm)	(32 ± 0.5) mm (total length of both arms)
Vertical stem diameter	(1.42–1.63) mm	Not specified	(1.5 ± 0.1) mm
Horizontal arms diameter	(1.50–1.65) mm	Not specified	(1.6 ± 0.1) mm

## Summary of Specification Changes

Attribute	Population Council	ISO 7439	WHO/UNFPA 2010
Frame junction radius	Not specified	Not specified	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 from 0.25 mm to 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 done 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.
Vertical stem-to-ball junction radius	Not specified	Not specified	The junction between the ball and the vertical stem shall preferably be radiused.
Ball end diameter	$(3 \pm 0.127)$ mm (2.873–3.127 mm)	Not specified	T piece ball (at end of vertical stem) diameter: $(3.00 \pm 0.70)$ mm
Ball end hole	Not specified	Not specified	T piece ball (at end of vertical stem) shall have a hole of maximum diameter 0.80 mm for securing the thread. The hole may be tapered or dumbbell-shaped.
Wire end hole	Not specified	Not specified	Optionally, a hole for anchoring an end of the copper wire may be provided. This hole must not reduce the breaking strength of the vertical stem below that specified in ISO 7439:2002, Clause 7: 7.3. The hole may be tapered or dumbbell-shaped, with a maximum diameter of 0.55 mm and placed $(2.8 \pm 0.15)$ mm from the intersection of the horizontal arm and vertical stem centrelines [equivalent to $(3.6 \pm 0.15)$ mm from top edge of the horizontal arm].
Memory	Maximum 5 mm after 1 minute's recovery from the 5-minute folded state.	Maximum 5 mm	Maximum 5 mm

Summary of Specification Changes			
Attribute	Population Council	ISO 7439	WHO/UNFPA 2010
Flexibility	A deflection between 4.8 and 6.5 units at $(24 \pm 1.5)^\circ\text{C}$ after 6 hrs equilibration and before 96 hrs after manufacture with correction factors 0.125 units per $^\circ\text{C}$ difference from $24^\circ\text{C}$ between $20^\circ\text{C}$ and $29^\circ\text{C}$ . After 96 hrs from time of manufacture, a deflection greater than 4.0 units.	Not specified	Retained, as in Population Council specification, but narrowing temperature range to $(23 \pm 2)^\circ\text{C}$ , after careful consideration following clarification of the units as mm and establishing that the test is feasible and the equipment defined.
<b>Copper</b>			
Surface area (wire plus sleeves)	380 mm <sup>2</sup>	(200 to 380) mm <sup>2</sup> $\pm 10\%$ tolerance (343–418) mm <sup>2</sup> ) to (200 to 380) mm <sup>2</sup> $\pm 10\%$ tolerance on nominal specified surface area	The total nominal active copper surface area, wire and collars shall be 380 mm <sup>2</sup> $\pm 10\%$ .
Copper wire on vertical stem–material	99.99% pure; table of impurities with ppm limits in specification	99.9% pure	Oxygen-free electronic (OFE) 99.99% pure copper (National Bureau of Standards designation UNS C10100)
Copper wire diameter	$(0.254 \pm 0.0051)$ mm (0.2489–0.2591) mm	$\pm 10\%$ tolerance (0.237–0.262 mm)	$(0.255. \pm 0.005)$ mm (30 AWG, 33 ISWG)
Copper wire weight on each T frame	165–187 mg	Not specified	The weight of wire on the frame shall be not less than 165 mg and not more than 187 mg.
Weight of 100 cm–length	436–472 mg	Not specified	<i>[The weight per 100 cm length requirement is dropped because the grade specification and the diameter provide adequate assurance without further specification.]</i>
Copper collars on each transverse arm–material	OFHC copper tube half hard temper, 99.99% pure	Not specified	Oxygen-free electronic (OFE) 99.99% pure copper (National Bureau of Standards designation UNS C10100) copper tube half hard temper
Copper collar surface area	<i>[Not specified separately in any specification or standard]</i>		
Copper collar weight	$(68.7 \pm 3.0)$ mg (65.7–71.7) mg	Not specified	$(68.7 \pm 3.0)$ mg
Copper collar length	$(5.03 \pm 0.127)$ mm (4.903–5.13) mm	Not specified	$(5.0 \pm 0.15)$ mm
Copper collar internal diameter	$(0.066 \pm 0.001)$ inches, metricated to $(1.676 \pm 0.0254)$ mm	Not specified	$(1.68 \pm 0.025)$ mm
Copper collar external diameter	$(0.0865 \pm 0.001)$ inches, metricated to $(2.197 \pm 0.0254)$ mm (2.1717–2.2224) mm	Not specified	$(2.2 \pm 0.025)$ mm

## Summary of Specification Changes

Attribute	Population Council	ISO 7439	WHO/UNFPA 2010
Copper sleeve external diameter after fixing	(0.082 ± 0.001) inches, metricated to (2.083 ± 0.0254) mm	Not specified	<i>[This requirement is dropped because of the differing effects of the methods of fixing the collar and the overriding requirement for adequate retention force.]</i>
Copper sleeve position	(5.4 ± 0.4) mm from the ends of the T horizontal arm	Not specified	Collar position: (5.4 ± 0.4) mm from the ends of the T horizontal arm
Copper collar retention force	Not specified	Not specified	The minimum force required to displace a collar on the arm shall be 6.86 Newton (700 g-force) when tested using a separation speed of (200 ± 20) mm/min.
Copper sleeve tensile strength	Not specified	Not specified	<i>[The previous UNFPA requirement of 0.46 and 2.0 lb has been dropped.]</i>
Copper sleeve finish	Not specified	Not specified	The collars shall be deburred, polished and free from sharp edges, for example, by barrel tumbling.
<b>Thread</b> (thread/suture) attached to base of vertical stem for removal of device			
Material	High-density linear polyethylene (high-density polyethylene—Philips Marlex 6006—containing up to 1% titanium dioxide)  Passing a rabbit implantation test.	Monofilament  Non-absorbable	The thread shall be monofilament made from high-density polyethylene (HDPE), free of stabilizers, having a sufficient minimum tensile strength to produce a thread meeting the specified strength requirement (9.5 Newton). A material with a minimum tensile strength ( <i>ASTM D6380, ISO 527-2</i> ) of 28 MPa is recommended.  The thread polymer shall be compounded with 0.4% up to 1.0% by weight of USP (EP) rutile titanium dioxide.  The compounded polymer (HDPE plus titanium dioxide) shall be evaluated for biological safety in accordance with <i>ISO 10993-1:2003</i> requirements for mucosal membrane contact devices intended for permanent contact. Specifically, the following testing is required:  <i>(continued)</i>

Summary of Specification Changes			
Attribute	Population Council	ISO 7439	WHO/UNFPA 2010
			<p>Testing for genotoxicity according to <i>ISO 10993-3</i></p> <p>Testing for cytotoxicity testing according to <i>ISO 10993-5</i></p> <p>Testing for irritation and delayed-type hypersensitivity according to <i>ISO 10993-10</i></p> <p>Testing for subacute and subchronic toxicity according to <i>ISO 10993-11</i></p>
Thread diameter	(0.010 ± 0.002) inches, metricated to (0.254 ± 0.051) mm	Not specified	The thread diameter shall be (0.25 ± 0.05) mm.
Thread length	(105–125) mm	Minimum 100 mm	The length of each tail shall be 105–125 mm.
Device breaking force	0.907 kg (8.89 N)	Minimum 1.224 kg (12 N)	When tested according to <i>ISO 7439:2002</i> , Clause 7 the peak load at break shall be greater than 9.5 Newton.
<b>Insertion tube</b>			
Material	High-density linear polyethylene	Not specified	High-density polyethylene (HDPE) food contact grade
Insertion tube length	(206.637 ± 1.587) mm (205.05 ± 208.224) mm	Not specified	(206 ± 2) mm
Insertion tube inner diameter	(3.70 ± 0.076) mm (3.624 ± 3.776) mm	Not specified	(3.7 ± 0.1) mm
Insertion tube outer diameter	(4.394 ± 0.1) mm (4.294 ± 4.494) mm	Maximum 5 mm	(4.4 ± 0.1) mm
Insertion tube density	(0.959–0.969) g/cm <sup>3</sup>	Not specified	[Deleted as unnecessary.]
<b>Moveable flange</b>			
Material	Polyvinyl chloride + titanium dioxide + FDC Blue	Not specified	Polymer with adequate radiation stability to function mechanically post-sterilization. Optionally, the flange may be pigmented.
Flange—diameter of centre hole	(4.089 ± 0.1) mm (3.989–4.189) mm	Not specified	(4.1 ± 0.1) mm  The shape and dimensions of the central hole may be changed to facilitate meeting the specified flange displacement force.
Flange displacement force	(0.209 to 0.907) kg	Not specified	Use a steadily applied displacement. The required force should fall between 2.0 and 9.0 Newton.
Flange location	Not specified	Not specified	Not specified

## Summary of Specification Changes

Attribute	Population Council	ISO 7439	WHO/UNFPA 2010
<b>Displacement Rod</b>			
Material	Polypropylene + 0.5% titanium dioxide	Not specified	Food contact grade radiation stable ABS (acrylonitrile-butadiene-styrene polymer) or food contact grade radiation stabilized polypropylene (PP) with a tip diameter of $(2.6 \pm 0.2)$ mm.  Optionally, the insertion rod may be pigmented.
Solid rod length—end stem to end tie	$(195 \pm 2.54)$ mm (192.46–197.54 mm)	Not specified	$(190 \pm 5)$ mm from handle brace to tip
Diameter of rod at tip	Not specified	Not specified	$(2.6 \pm 0.2)$ mm
Solid rod diameter	(2.540–2.743) mm	Not specified	Not specified
<b>Sealed sterile package</b>			
Material	Laminated polyethylene/Mylar and Tyvek 1073B	Not specified	Packaging materials shall comply with <i>ISO 11607–1:2006</i> .  Polymer films shall be used, preferably continuous to reduce the risk of copper tarnishing.
Package sterilization	Ethylene oxide	Ethylene Oxide Radiation (Gamma or Electron Beam)	Sterilization shall be by radiation according to <i>ISO 11137</i> series or by ethylene oxide according to <i>ISO 11135</i> series and standards normatively referenced therein.
Package sterility	Assessed by incubation of packages according to USP XXI using 10 packages containing <i>Bacillus subtilis</i> spore strips (106 spores per strip) and 20 standard packages.	Not specified	The sterilization assurance level shall be $10^{-6}$ .
Package shelf-life	Not specified	Not specified	The maximum permitted shelf-life for storage of the device prior to insertion is five years. This defines the “ <b>Latest Insertion Date</b> ” (LID).  Shelf-life claims shall be supported by appropriate stability data. Guidance on conducting stability studies is given in Annex V: Accelerated Ageing Testing.  (continued)

Summary of Specification Changes			
Attribute	Population Council	ISO 7439	WHO/UNFPA 2010
			When conducting stability studies, manufacturers shall include products assembled from components that have been stored for the maximum component storage periods specified by their manufacturers.
Package marking	Not specified	Not specified	Information required in accordance with <i>ISO 7439</i> , including information intended for the end user, shall be provided in accordance with the contractual requirements agreed with the purchaser (see Section 1, Chapter 1, Clause 8.4 for full details).
Package peeling force	Minimum 0.453 kg/2.5 cm	Not specified	When tested according to <i>ASTM F88:2000</i> (standard test method for seal strength of flexible barrier materials), the peel force shall be not less than 4.4 N/2.54 cm and not greater than 19 N/2.54 cm.
Package dimensions	Not specified	Not specified	Not specified
Package integrity	Not specified	Not specified	Sealed pouch integrity shall be tested according to <i>ASTM D3078:1994</i> (standard test method for determination of leaks in flexible packaging by bubble emission).  If permeable packaging material is used, sealed pouch integrity shall be tested according to <i>ASTM F1929:2004</i> (standard test method for detecting seal leaks in porous medical packaging by dye penetration).
Workmanship	Not separately specified in detail	Not specified	Section listing major and minor defects added.



## ANNEX III

### SUMMARY SPECIFICATION FOR COPPER PURITY

Summary Specification for Copper Purity	
Impurity	Maximum (%)
Ag	0.0025
As	0.0005
Bi	0.0001
Cd	0.0001
Fe	0.0010
Mn	0.0001
Ni	0.0010
O <sub>2</sub>	0.0005
P	0.0003
Pb	0.0005
S	0.0015
Sb	0.0004
Se	0.0003
Sn	0.0002
Te	0.0002
Zn	0.0001

## ANNEX IV

# RECOMMENDATIONS TO ISO TECHNICAL COMMITTEE 157 PREPARING THE INTERNATIONAL STANDARD ISO 7439 COPPER-BEARING INTRAUTERINE DEVICES

The international standard for copper-bearing IUDs is currently being updated, and WHO was asked to respond to a number of issues concerning efficacy, safety and performance, which were raised by members of the working group updating the standard.

In response to this request the WHO/UNFPA Technical Review Committee discussed whether to change the limit specified for a one-year pregnancy rate from less than or equal to 2 per hundred women to less than or equal to 1 per 100 and noted that two devices, the TCU200 and Copper 7 (no longer available) have reported pregnancy rates at the end of one year with point estimates that exceeded 2. The group also felt that the upper limit on the 95% confidence interval is a better criterion than the point estimate, since the confidence interval is dependent on the size of the study population and the number of events.

In light of these considerations, the Technical Review Committee recommended the following amendments to sections 4, 5, 7, and 11 of *ISO 7349*:

### Section 4.2. Clinical performance

An IUD shall meet the following requirements:

- The upper limit of the two-sided 95% confidence interval for the one-year pregnancy rate computed using life-table methods shall be less than or equal to 2%.
- One-year expulsion rates computed using life-table methods shall be less than or equal to 10%.
- One-year discontinuation rates computed using life-table methods shall be less than or equal to 35%.

### Section 7.7. Clinical evaluation

This section should be changed using the following information:

Contraceptive efficacy rates should be determined in a randomized controlled equivalence or non-inferiority trial using the TCU380A as the control device. Appropriate sample sizes should be used to ensure that the pregnancy rate criterion specified above can be

met. Any trial shall include at least 20,000 woman-months for the device under test.

As a minimum requirement manufacturers may demonstrate compliance with this standard by conducting a randomized study in which an average of 720 women use the test device in the first year of the study and an average of 360 women in a control arm use the TCU380A device.

A study with an average of 720 women followed during the first year of use and a true pregnancy rate of 1% would have an approximate two-sided 95% confidence interval for the first-year pregnancy rate of 0.4%–2.0%. Depending on the attrition rate in the study cohort, this number of women completing the first year could be achieved by enrolling between 900 and 1,000 women.

The control arm using the TCU380A IUD shall be included in the trial to confirm that no bias is introduced due to the study methodology and/or the population using the index device. This can be demonstrated if an average of 360 women are followed during the first year of use. Assuming a true pregnancy rate of 1% for the TCU380A IUD, the approximate two-sided 95% confidence interval for the first-year pregnancy rate would be 0.2%–2.7%. Depending on the attrition rate in the control cohort, this could be achieved by enrolling between 450 and 500 women. Hence, the upper limit of the two-sided 95% confidence interval for the TCU380A should be no greater than 2.7%.

**Note:** A randomized controlled study designed as an equivalence trial with an average of 720 women using the test device and 360 women in the control arm would declare as equivalent two devices for which true pregnancy rates are 1% if the difference in observed pregnancy rates was  $\leq 2.1$  percentage points. Therefore, a study of this size would have very limited power.

### Section 5.3.2. Copper components

The nominal active surface area of copper shall be at least 200 mm<sup>2</sup>.

#### **Section 5.3.4. Insertion instrument**

Any changes to the inserter or the insertion technique have to be justified.

#### **Section 5.5.1. Shelf-life stability**

Manufacturers shall undertake real-time *in vitro* studies.

#### **Section 5.5.2. *In situ* stability**

Amend to read: “During the length of its intended use, the frame together with the copper components . . .”

#### **Other recommendations:**

In Section 7.7, under the subheading “Following the removal of an IUD, the following data shall be collected for a representative sample:”, add the following:

Length of use:

Remove instructions describing “self-check” and “self examination” from sections 7.7 and 11.5, respectively.

Section 11.2. Labelling of the primary container:

The packaging for the device should make a clear distinction between the expiration date of the sterilized product and the duration of activity, which dates from the time of insertion.

Section 11.4. Instructions for use: As there is no evidence of an increased risk, remove: “slightly increased risk of perforation when an IUD is inserted in a woman who is fully breastfeeding.”

## ANNEX V

### ACCELERATED AGEING TESTING

#### 1. Introduction

Accelerated ageing is performed on packaged medical devices to estimate shelf-life and document product expiry dates and maximum storage temperatures. Real-time ageing is still necessary for many medical devices, including IUDs, to confirm provisional shelf-life estimates determined using accelerated procedures. 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.

In the case of copper-bearing IUDs manufacturers must determine the **Latest Insertion Dates** from the time of manufacture. In this annex this time period is referred to as the shelf-life.

It is recommended that design and analysis of accelerated ageing testing be based on the Arrhenius equation (1), which describes the relationship between the rate of change of a chemical process and temperature. Very useful guides to the practical application of the Arrhenius equation to accelerated ageing studies are given in *ISO 11346:2004 Rubber, Vulcanized or Thermoplastic—Estimation of Life-time and Maximum Temperature of Use*, and *EN 455-4. Medical Gloves for Single Use—Part 4: Requirements and Testing for Shelf-life Determination*, March 2009.

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. 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 kJ/mole to over 200 kJ/mole. 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.

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. Accelerated studies should be referenced back to this temperature. This means that 30 °C should be used as the standard temperature for all stability studies on IUDs intended for public-sector distribution (2). The specified relative humidity for climatic zone IV (hot and humid) is currently 65%. Although relative humidity is unlikely to have any effect on the properties of the IUD directly, pack seal could be affected. For this reason real-time stability studies should be conducted at a relative humidity of 65% or higher.

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 the relatively low activation energy of 78 kJ/mole to calculate the ageing periods means that the estimated shelf-life will be conservative. In practice, therefore, shelf-lives are likely to be longer than five years at 30 °C if products remain in compliance 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.

#### 2 Terms and definitions (3, 4)

For the purposes of this document, the following terms and definitions apply. They have been modified from definitions in *EN 455-4 Medical Gloves for Single Use—Part 4: Requirements and Testing for Shelf-life Determination*, March 2009, and *ISO 11346:2004 Rubber, Vulcanized or Thermoplastic—Estimation of Life-time and Maximum Temperature of Use*.

##### 2.1 Arrhenius equation

The Arrhenius equation describes the relationship between the activation energy ( $E_a$ ), the absolute

temperature ( $T$  expressed in °K), and the rate constant of a degradation reaction [ $k_{(T)}$ ].

**Note:** The shelf-life of a product is predicted based on the Arrhenius principle of chemical reaction rates. The Arrhenius equation has the basic form:

$$k_{(T)} = A e^{\frac{-E_a}{RT}}$$

Where:

$A$  = pre-exponential factor ( $s^{-1}$  for first order reactions)

$E_a$  = Activation energy (J/mole)

$R$  = the Universal Gas Constant ( $8314 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$ )

$T$  = Absolute temperature (K)

$k_{(T)}$  ( $s^{-1}$  for first order reactions) is the rate constant for the degradation process.

An alternate way of expressing the Arrhenius equation is:

$$\ln k_{(T)} = \ln A - \frac{E_a}{RT}$$

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 °K) 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  $E_a/RT$ .

## 2.2 Individual package

The package, intended for distribution to a clinician, containing the IUD.

**Note:** For example, a primary pack (peel pack) for a sterile product.

## 2.3 Latest insertion date

Stated date after which the IUD shall not be inserted.

## 2.4 LOT

A population of IUDs manufactured at essentially the same time, using the same process, raw materials of the same specifications, and common equipment and packed in the same type of individual container.

## 2.5 Shelf-life

Time from date of manufacture to the claimed Latest Insertion Date.

## 2.6 Significant change

Change that could reasonably be expected to affect the safety or effectiveness of a medical device.

**Note:** This could include a change to any of the following:

- a) the manufacturing process, facility or equipment;
- b) the manufacturing quality control procedures, including the methods, tests or procedures used to control the quality, purity and sterility of the device or of the materials used in its manufacture;
- c) the design of the device, including its performance characteristics, principles of operation and specifications of materials;
- d) the intended use of the device, including any new or extended use, any addition or deletion of a contraindication for the device and any change to the period used to establish its latest insertion date.

## 2.7 Specification limit

Maximum or minimum value for a property being tested.

## 2.8 Life-time

Time at which the material under test has reached the specified threshold value for the property tested at the temperature of use.

## 2.9 Maximum temperature of use

Temperature at which the material under test has reached the specified threshold value for the property tested after the specified time.

## 2.10 Mean kinetic temperature

A single derived temperature that, if maintained over a defined period, would afford the same thermal challenge to a pharmaceutical product as would have been experienced over a range of both higher and lower temperatures for an equivalent defined period (5).

### 2.11 Threshold value

Particular degree of degradation that is taken as the maximum acceptable for the property being tested.

**Note:** The time to reach the threshold value can be used to represent the reaction rate.

## 3 Method

### 3.1 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.

### 3.2 Arrhenius analysis

The method recommended in this annex is based on *ISO 11346:2004 Rubber, Vulcanized or Thermoplastic—Estimation of Life-time and Maximum Temperature of Use*, with a standard temperature of 30 °C.

### 3.3 Equipment

Oven or other temperature-controlled container.

*ISO 188:2007* specifies accelerated ageing or heat resistance tests on vulcanized or thermoplastic rubbers. Two methods are given:

**Method A:** Air-oven method using a cell-type oven or cabinet oven with low air speed and a ventilation of 3 to 10 changes per hour;

**Method B:** Air-oven method using a cabinet oven with forced air circulation by means of a fan and a ventilation of 3 to 10 changes per hour.

The oven equipment and air changes shall be specified and can be of either type but must be consistent from experiment to experiment and within an experiment.

### 3.4 Hygrometer

The instrument used to indicate the relative humidity shall be accurate to  $\pm 2\%$  relative humidity. A

psychrometer may be used either for direct measurement of relative humidity or for checking the hygrometer (6).

### 3.5 Test items

Samples from normal production made using normal production equipment and processes (including packaging equipment) and 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.

### 3.6 Use of retained samples

It may be of value to consider using any retained samples that already have 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.

### 3.7 Test sample size

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

### 3.8 Critical performance and product package measurements

Critical performance measurements (CPM) that should be monitored during stability studies are:

- T frame strength at break
- thread tensile strength.

Critical product package measurements (CPPM) that should be monitored are:

- pack integrity (at the longest time at each temperature only and in real-time study at each year);
- peel strength (at the longest time at each temperature only and in real-time study at each year).



## 4 Test protocol

The following temperatures and ageing periods shall be used:

Temperatures and ageing periods for Critical Product Measures (CPM) and Critical Product Package Measures (CPPM)—accelerated ageing			
Temperature	Ageing periods at specified temperature (tests to be conducted)		
80 °C	1 week (CPM)	2 weeks (CPM)	4 weeks (CPM, CPPM)
70 °C	2 weeks (CPM)	4 weeks (CPM)	8 weeks (CPM, CPPM)
60 °C	5 weeks (CPM)	10 weeks (CPM)	16 weeks (CPM, CPPM)
50 °C	12 weeks (CPM)	24 weeks (CPM)	40 weeks (CPM, CPPM)
40 °C	30 weeks (CPM)	60 weeks (CPM)	100 weeks (CPM, CPPM)

Ageing periods for Critical Product Measures (CPM) and Critical Product Package Measures (CPPM)—real time ageing at 30 °C					
30 °C—Real-time study	1 year (CPM, CPPM)	2 years (CPM, CPPM)	3 years (CPM, CPPM)	4 years (CPM, CPPM)	5 years (CPM, CPPM)

The relative humidity (RH) for the accelerated ageing and real-time studies shall be maintained at 65% RH or more (International Conference on Harmonization conditions for climatic zone IV) at 30 °C. At elevated temperatures a humidity of at least 65% RH at the ageing temperature shall be maintained.

## 4.1 Measurements

The measurements shall include full packaging and finished product characterization as per the revised *WHO/UNFPA TCu380A IUD Specification*.

Strength measurements are carried out using the amended “arms-up” method from the new revised *WHO/UNFPA TCu380A IUD Specification*, shown in Appendix VII. 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.

## 4.2 Significant change

All test results shall be in compliance with the revised *WHO/UNFPA TCu380A IUD 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 or thread strength shall be taken as an indication that the acceptable shelf-life of the product has been exceeded even if the force at break properties comply with the specification.

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 All 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 non-compliant 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.

- **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, then it can be concluded with a high degree of confidence that the shelf-life is in excess of five years.
- **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 °K).

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 based on the WLF (William Landel-Ferry theory, also known as the time/temperature superposition equation) described in *ISO 11346* to analyse the data. (Assistance will probably be required to do this analysis.)

- **A critical performance measurement deteriorates by 25% or more within the times periods specified in the table:** 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.

## 7 Real-time ageing study shelf-life estimate

A real-time ageing study shall be commenced at the same time as the accelerated study, 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.

### References

1. Arrhenius S. *Z Phys Chem*, 1889; 4:226 and 1899; 31:187.
2. World Health Organization. Working document QAS/06.179 (Restricted). Stability testing of active substances and pharmaceutical products.
3. *EN 455–4 Medical gloves for single use—Part 4: Requirements and testing for shelf-life determination*.
4. *ISO 11346 Rubber, vulcanized or thermoplastic—Estimation of life-time and maximum temperature of use*.
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. (<http://www.ich.org>).
6. *ASTM F1980–07 Standard guide for accelerated ageing of sterile barrier systems for medical devices*.

## Applicable Standards

*EN 455–4 Medical Gloves for Single Use—Part 4: Requirements and Testing for Shelf-life Determination*.

*ISO 7439 Copper-Bearing Intrauterine Devices*.

*ASTM F1980–07 Standard Guide for Accelerated Ageing of Sterile Barrier Systems for Medical Devices*.

*ISO 188 Rubber, Vulcanized or Thermoplastic—Accelerated Ageing and Heat Resistance Tests*.

*ISO 11346 Rubber, Vulcanized or Thermoplastic—Estimation of Life-time and Maximum Temperature of Use*.

*WHO Working Document QAS/06.179 (Restricted). Stability Testing of Active Substances and Pharmaceutical Products*.

*ISO 13485 Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes*.

*ISO 10012 Measurement Management Systems—Requirements for Measurement Processes and Measuring Equipment*.

## ANNEX VI

# ASSESSMENT OF USED TCU380A IUDS FOR EVIDENCE OF AGEING IN USE

## 1 Summary

To examine effects of ageing *in utero*, used TCU380A IUDs were obtained from routine removals in clinics in five countries. The intent was to determine if ageing during storage and *in utero* has any effect on the physical properties of the IUD. An improved clamping configuration and clamp design were developed for the strength tests, which may be of benefit to manufacturing quality control.<sup>1</sup> Results showed no time-related ageing effects *in utero*, but mean strengths were on average 77% of the value for the controls. In addition, results showed that radiusing, particularly at the junction between the horizontal and vertical stem (but also at the wire insertion hole and vertical stem-to-ball junction) to reduce stress concentrations at these points should be considered, subject to confirmation that introducing the radius does not increase the risk of damage to the junction when the IUD is loaded into the insertion tube.

No significant loss in strength of frames was found during ageing *in utero*. However, cracks were found propagating slowly and cyclically in armpit regions. Although these cracks could possibly be propagated further during removal through the cervix, frames that were measured had adequate residual strength. Age-related loss of thread strengths at their vaginal end was suggested by the data, although measurements were difficult. Incomplete barium sulphate pigment dispersion, as seen in most frames, was a potential source of infrequent, random, non-age-related breakages. Consideration should be given to improving dispersion quality control methods or to removing barium sulphate altogether. “Survivor bias” would have obscured breakages caused by poor barium sulphate dispersion, and none were observed in this work. Copper wire loss rate was found to be highly variable, ranging from 0% at eight years to 100% at six years.

## 2 Background

The author was aware of a number of issues with IUD specifications from participation in a number of

failure analyses of broken frames and threads in the late 1980s and from his continued involvement in IUD manufacturing development to the mid-1990s. Additionally, potential concerns were raised about the oxidative stability of the polymer frame and thread used, since these materials are compounded without antioxidants and the method of sterilization is now largely by radiation rather than ethylene oxide as originally specified by the Population Council.

A 2007 Cochrane Review had concluded that:

- The pregnancy rate for the TCU380A was in the range 0 to 1% after one year.
- The “expulsion rate” was in the range 2.4% to 8.2% after one year.
- “Total medical discontinuations” in non-Chinese centres was 52% over 10 years.

Although these rates compare favourably with those of other copper-bearing IUDs and other contraceptive methods, it was considered that reduction in expulsion and discontinuation rates might be possible if the performance of the device could be improved by changes to the specification. For example, in some cases expulsions may have been associated with frame breakages, and some pregnancies may have resulted from unrecognized expulsions.

The subsequent work by Nazar Associates Inc. focused on design issues affecting the strength of both the polyethylene T frame and the polyethylene monofilament removal threads. The following potential causes of premature failure were identified:

- unspecified radiuses on the frame
- oxidative damage to the unstabilized polymer of both frame and thread
- imperfections in the dispersion of barium sulphate in the frame compound.

## 3 Process

1. The publicly available literature on breakages of copper-bearing TCU380A IUDs was reviewed. This

<sup>1</sup> The revised improved clamping configuration and clamp design has been incorporated into the strength test in the *WHO/UNFPA TCU380A IUD Specification*.

- included both case reports and research papers in which ageing of TCu380A IUDs was examined.
2. New unused TCu380A IUDs were obtained for use as “controls”.
  3. Methods were developed for measuring the tensile strength of the frame in an “arms-up” geometry to approximate the deformation during removal through the cervix.
  4. Methods were developed for measuring strength of threads separately from that of the frames, including a gripping method suitable for short threads.
  5. A protocol for sterilizing removed TCu380A IUDs was developed.
  6. The selected sterilization method was shown to have no effect on strength—neither of control frames, nor control threads.
  7. Used TCu380A IUDs were obtained from routine removals at clinics in Bolivia, Kenya, Philippines, United Kingdom and Viet Nam and sterilized using the protocol developed (item 5). Data on the age of the IUD and reason for removal were collected.
  8. On receipt by Nazar Associates, used TCu380A IUDs were photographed through the transparent packaging and then again on first removal from packaging. Age data, etc. supplied by the clinics was recorded in spreadsheet format. TCu380A IUDs were then sterilized again (per protocol) and re-packaged in new individually labelled packages (total of 73 used specimens).
  9. Each sterilized IUD was optically scanned at 2400 pixels/inch. Magnified images were examined for damage. Three visibly, partially fractured TCu380A IUDs were separated from the remainder.
  10. Tensile strengths of 40 used frames were measured in a selection across the age distribution, using the “arms-up” test apparatus pulled at 200 mm/min in an Instron equipped with 1000 N load cell. Strengths were plotted against age *in utero* for trends and for comparison with controls.
  11. Tensile strengths of used threads were measured in a selection of older and newer specimens, pulling a total of 31 threads at 200 mm/min with an Instron equipped with 1000 N load cell. Grip separation was typically about 2 cm. Break locations (uterine end versus vaginal end) were recorded. Strengths (of those that did not slip) were plotted against age *in utero*. Evidence for a gradient of oxidative damage was sought from break locations.
  12. Copper wire was removed from the vertical stems of 29 used TCu380A IUDs chosen across the full age distribution. These TCu380A IUDs had not been tensile-tested. Weight of copper wire was plotted against age *in utero*.
  13. The 29 used TCu380A IUDs without copper wire were X-rayed at 35 kV using fine-grained industrial X-ray film. The developed film was scanned at 2400 pixels/inch, and then scans were visually inspected with the aid of size standards. Barium sulphate agglomerates were counted by size category.
  14. A selection of used TCu380A IUDs was examined by scanning electron microscopy. This selection included as-received frames, experimentally broken frames, frames from the X-ray examination having apparent barium sulphate agglomerates and voids, and used threads’ uterine and vaginal ends.
  15. All specimens and original images have been retained.

#### 4 Outcomes

1. The literature suggested a low but persistent level of breakages and a few clusters. Breakages may be under-reported. One group reported a strong correlation of declining mechanical fatigue resistance with duration *in utero*.
2. The “arms-up” strength test assessed frame and thread separately, and it imposed a stress pattern akin to final removal through the cervix. It was an improvement on the existing *ISO 7439* method.

3. Copper-loss measurements were not an objective of this work, but wire was removed in preparation for X-rays of frames, and these wires were weighed. Some TCu380A IUDs' wire windings were completely gone as early as 5.8 years *in utero*, but others were still at starting weight after more than eight years. Mean wire loss rate was about 12 mg/year. Copper sleeves, both clinched-on and moulded-on, remained longer, perhaps because they were attached better, or were thicker, or were in a lower-oxygen environment. The weights of the copper sleeves were not measured. Therefore, it was not possible to estimate the rate of loss of copper from the sleeves.
4. IUD frames showed no time-related ageing effects, but the mean strengths were on average 77% of the value for the controls. There was no overlap between used and control groups' strengths. The lowest used IUD strength was 25.5 N (5.7 lbf). The mean was 30.0 N. The mean age was 6.0 years *in utero*, and the span was from one month to 16 years. The implication was that oxidative ageing was insignificant *in utero*, but oxidative damage between manufacture and insertion cannot be ruled out. However, better radiusing may have contributed in whole or part to greater strength of the controls. See item 5, below.
5. The weakest locations on the used frames were armpits (29 breaks) followed by wire insertion holes (4 breaks) and ball-to-vertical stem junctions (3 breaks). Sleeves pulled off in three cases, one of which was simultaneous with armpit fracture, counted previously.
6. The controls were radiused better at armpits. Presumably as a result, only 3 of 19 breaks in control IUDs were at armpits. Breakage at the ball-to-vertical arm junction dominated (10 breaks), followed by wire holes (six breaks). Obviously, there would be benefits to careful radiusing at all stress-riser features. Manufacturers intending to make the change must evaluate the impact of adding a radius at the junctions of the arms on the risk of damage occurring when the IUD is loaded into the insertion tube.
7. Minor cracking was observed in used, un-tested frames at the armpit region. In a few cases cracking was visually apparent. Cracking was visible in many more cases at higher magnification—but not in every case, even for older, used TCu380A IUDs. Nevertheless, strength retention was satisfactory.
8. Old fracture origins had multiple bands parallel to fracture edges. These indicated cyclic crack growth, presumably from cyclic uterine events. Surfaces of polymer appeared brittle, but deeper material remained ductile, accounting for the strength retention. New crack surfaces caused by fast tear during removal through the cervix, or created by tensile testing, were visually different from old fracture origins.
9. IUD thread strengths showed a weak ageing effect but not sufficient to require changes to the specification. The extreme vaginal ends of threads appeared more degraded and weakened than higher up, as expected for an oxygen gradient from vagina to uterus. Measurements suggesting this were for high statistical quality, however.
10. Un-dispersed barium sulphate was observed in X-rays of most but not all frames. Agglomerates (clusters of small particles) 150 micrometers and smaller were usually too numerous to count. The size distribution extended to as large as 800 micrometers (0.8 mm). Bonding between barium sulphate particles and polymer was non-existent. There is a risk that the agglomerates of barium sulphate could act as mechanical flaws and initiate fracture if located at a highly stressed region, such as the junction between the horizontal arm and vertical stem.
11. No breaks were found associated with undispersed barium sulphate in the microscopy. This was inconclusive, because agglomerates at highly stressed areas (e.g. armpits) would be expected to cause early breakage and expulsion, and so these hypothetical cases would not be among the used TCu380A IUDs supplied by the clinics. Predictably, no undispersed barium sulphate agglomerates were found in highly stressed zones of the used TCu380A IUDs.



## ANNEX VII

### STRENGTH TESTING METHOD

#### 1 Breaking strength

Sampling shall be in accordance with *ISO 2859-1*, Inspection Level G-1.

Manufacturers and testing laboratories may opt to sample in accordance with *ISO 3951-1* using the same Inspection Level and AQL. In cases of dispute, sampling according to *ISO 2859-1* shall be used.

Compliance shall be with an AQL of 1.0.

When pulled at 200 mm/minute, according to *ISO 7439:2002* Clause 7.3 as modified below, the breaking force of the finished product after sterilization shall be greater than 9.5 Newton.

Temperature during testing must be  $(23 \pm 2) ^\circ\text{C}$ . Conditioning as specified in *ISO 7439:2002* needs to be carried out only in cases of dispute.

When conducting the tensile test, the T frame shall be clamped by the copper collars (only) on the horizontal arms, using a gripping fixture that deforms the arms simultaneously parallel to each other and to the vertical stem, with horizontal arms  $(8.0 \pm 0.25)$  mm apart, centre-line to centre-line. The T junction must be unconstrained by the clamp. See Photo 1, below.

A convenient grip consists of two parallel grooves milled in a plate, which is then attached to one jaw of a common toggle clamp. See Photo 2, below. The grooves are milled with a 1/16 inch (1.59 mm) ball end mill to a depth of 1.38 mm, or about 65% of the collar diameter,

to ensure the collars stay in the grooves until the toggle clamp can be closed. The opposing jaw of the toggle clamp has a flat plate attached, parallel to the plane of the grooved plate when closed.

When mounting the toggle clamp to the test machine care should be taken that the axis of pull is co-linear with the vertical stem of the T. Note the alignment in Photo 2 of the threaded rod welded to the toggle clamp.

In use, the toggle clamp should be sufficiently tightened to prevent slippage but not so tight that it fully crushes the collars.

The ball end of the frame shall be gripped between two plates, into which are milled hemispherical cavities and half-cylindrical channels for the vertical stem. See Photos 3 and 4, next page. One of the plates is attached to a threaded rod for mounting to the tensile machine. To hold the plates closed, a 3/4-inch Kant-Twist™ clamp has been used, but any convenient clamp could be used, such as a second toggle clamp.

The intent is to have neither the ball cavity nor the vertical stem channel interfere with (grip) the ball or vertical stem, respectively, and so there should be a slight clearance for both. Ball nose end mills of 1/8-inch and 1/16-inch diameters were used to cut the hemispherical cavities and half-cylindrical channels.

It is critical that the junction of the metal between vertical stem channel and ball cavity be smoothly radiused on both faces, as shown. Nevertheless, some breaks at the vertical stem-to-ball junction may be expected in some

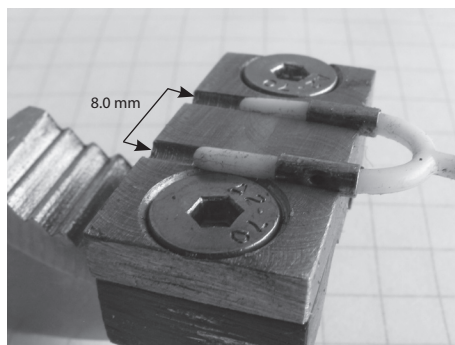


Photo 1. Arm Geometry



Photo 2. Grip overview

TCu380A IUD production, because of sharp junctions left in the plastic by some manufacturers.

It has been found convenient to remove the thread before testing; but if the thread must remain attached to the frame, a relief channel may be added on one face so that the thread does not prevent the two faces from closing on each other. This is shown in Photo 3.

For thread testing a pair of film grips with parallel flat rubber faces has been found satisfactory, if well-tightened. For gripping threads shorter than about 3 cm, firmly tightened toggle clamps having faces cushioned by approximately 1.0 mm thick rubber sheets of about 92 Shore A have been found satisfactory. Hydrogenated nitrile rubber has been found to have good wear resistance and grip.

Any tensile test should be rejected if breakage of the thread occurs at the entry to the grip.

The location of failure for any device failing the minimum strength requirement shall be noted (typically the vertical stem-to-ball junction, the wire insertion hole in the vertical stem or the junction between the vertical and horizontal arms).

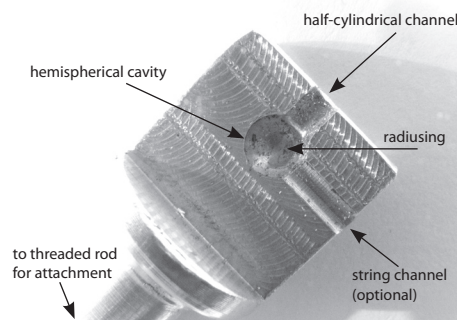


Photo 3

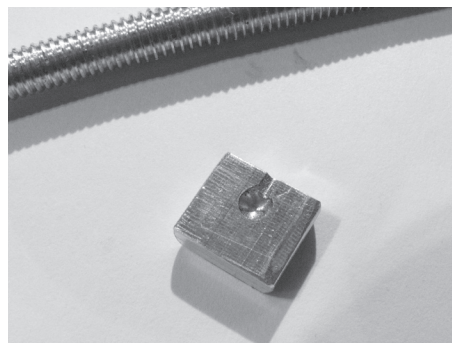


Photo 4



## ANNEX VIII

### GLOSSARY OF TERMS AND ABBREVIATIONS

<b>ABS</b>	Acrylonitrile-butadiene-styrene polymer.
<b>Acceptance number</b>	The highest number of non-compliers (failures) allowed in a specific test from a selected sample.
<b>AQL</b>	Acceptable Quality Limit. The quality level that is the worst tolerable process average when a continuing series of LOTS is submitted for acceptance sampling ( <i>ISO 2859-1</i> ). N.B. Manufacturers should be consistently achieving a process average that is better than the AQL.
<b>ASTM</b>	American Society for Testing Materials.
<b>AWG</b>	American wire gauge.
<b>Batch</b>	A term sometimes used in place of “LOT” (see definition of LOT). WHO recommends “LOT” be used when referring to medical devices. “Batch” also can refer to a quantity of individual raw materials.
<b>Bid security</b>	A guarantee from a bank that the bidder will perform its obligations in regard to the bid.
<b>Bioburden</b>	The population of micro-organisms on a raw material, a component, product, packaging or equipment.
<b>CE mark</b>	On medical product packaging, a mark certifying that the product conforms to the essential requirements of the European medical device directive 93/42/EEC.
<b>CPM</b>	Critical performance measurement.
<b>CPPM</b>	Critical product package measurement.
<b>Critical defects</b>	Defects that might affect the safety, acceptability and/or effectiveness of the product are classified as critical defects, causing the device to be rejected.
<b>DFID</b>	Department for International Development, UK.
<b>EOI</b>	Expression of Interest.
<b>EP</b>	European Pharmacopeia.
<b>Expiry date</b>	The date after which raw materials, components, etc. are no longer considered acceptable for manufacturing IUDs.
<b>FHI</b>	Formerly Family Health International.
<b>Forecast</b>	An assessment of the future requirements of a programme, based on historical trends, research or feedback from field workers on current needs.
<b>GMP</b>	Good Manufacturing Practice. A code of practice aimed at ensuring that product is consistently manufactured to the required standard.
<b>HDPE</b>	High-density polyethylene.
<b>HIV</b>	Human immunodeficiency virus.
<b>ICH</b>	International Conference on Harmonization.

<b>Inspection level</b>	The degree of examination of the LOT, as specified in <i>ISO 2859-1</i> . The higher the inspection level, the more samples that will be tested, and hence the lower the risk of faulty products reaching the consumer.
<b>IPPF/ICON</b>	International Planned Parenthood Federation/International CONtraceptive & SRH Marketing Ltd.
<b>ISO</b>	International Organization for Standardization.
<b>ISWG</b>	Imperial standard wire gauge.
<b>IUD</b>	Intrauterine device.
<b>Latest Insertion Date (LID)</b>	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 at which the device has to be removed from the uterus. The use of “expiry date” is therefore discouraged.)
<b>L/C</b>	Letter of Credit.
<b>LMIS</b>	Logistics Management Information System.
<b>LDPE</b>	Low-density polyethylene.
<b>LOT</b>	A quantity of products, such as IUDs, manufactured under essentially the same conditions. With certain exceptions, all the IUDs comprising a LOT will have single batches of components and be manufactured on the same production line and be sterilized under the same conditions over a single continuous series of dates.
<b>LOT number or code</b>	A unique identifying alphanumeric code assigned to a LOT.
<b>National Regulatory Authority (NRA)</b>	A regulatory body with authority in a specific country to control the importation and distribution of medical products. See also <i>Regulatory authority</i> .
<b>Non-critical defects</b>	Defects that might affect the acceptability of the product, causing the device to be rejected at the time of insertion, but are not expected to affect safety or effectiveness of the device.
<b>OFE</b>	Oxygen-free electronic.
<b>OFHC</b>	Oxygen-free high conductivity.
<b>Package</b>	The film-film or film-Tyvek peel pouch in which the IUD is sealed after manufacture and sterilization.
<b>PD</b>	Product Dossier.
<b>PP</b>	Polypropylene.
<b>Prequalification</b>	The steps taken by the buyer to verify a manufacturer’s suitability to provide IUDs of the required quality. The WHO/UNFPA Prequalification Scheme includes periodic assessment of manufacturing dossiers, testing of samples and factory inspection.

<b>Process average</b>	The percentage of non-conforming IUDs over a defined time period or quantity of production. It is calculated for each requirement detailed in the <i>WHO/UNFPA Specification</i> by dividing the number of non-conforming 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.
<b>Random sample</b>	A sample of IUDs drawn randomly from a LOT for testing purposes.
<b>Regulatory authority</b>	A national or international body set up to oversee the safety, efficacy and quality of medical devices, including IUDs, manufactured or imported and distributed within a country or region.
<b>Rejection number</b>	The number of non-compliers (failures) in a test sample that will cause a LOT to be rejected.
<b>RH</b>	Relative Humidity.
<b>RHCS</b>	Reproductive Health Commodity Security.
<b>RHSC</b>	Reproductive Health Supplies Coalition.
<b>Sampling plan</b>	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).
<b>Shelf-life</b>	The period of time after manufacture that the product is considered suitable for insertion, stated as the Latest Insertion Date on the pack.
<b>SMF</b>	Site Master File summary.
<b>SOP</b>	Standard operating procedure.
<b>Specification</b>	A detailed statement of a product's requirements as established by the buyer. Usually, a specification is based on an established standard.
<b>Standard</b>	A detailed statement of the minimum acceptance requirements, as established by a national or international regulatory body.
<b>UNFPA</b>	United Nations Population Fund.
<b>USAID</b>	United States Agency for International Development.
<b>USFDA</b>	United States Food and Drug Administration.
<b>USP</b>	United States Pharmacopeia.
<b>WHO</b>	World Health Organization.
<b>WHO/RHR</b>	World Health Organization, Department of Reproductive Health and Research.

# ANNEX IX

## IUD TECHNICAL DRAWINGS

Figure 1. T frame—landscape

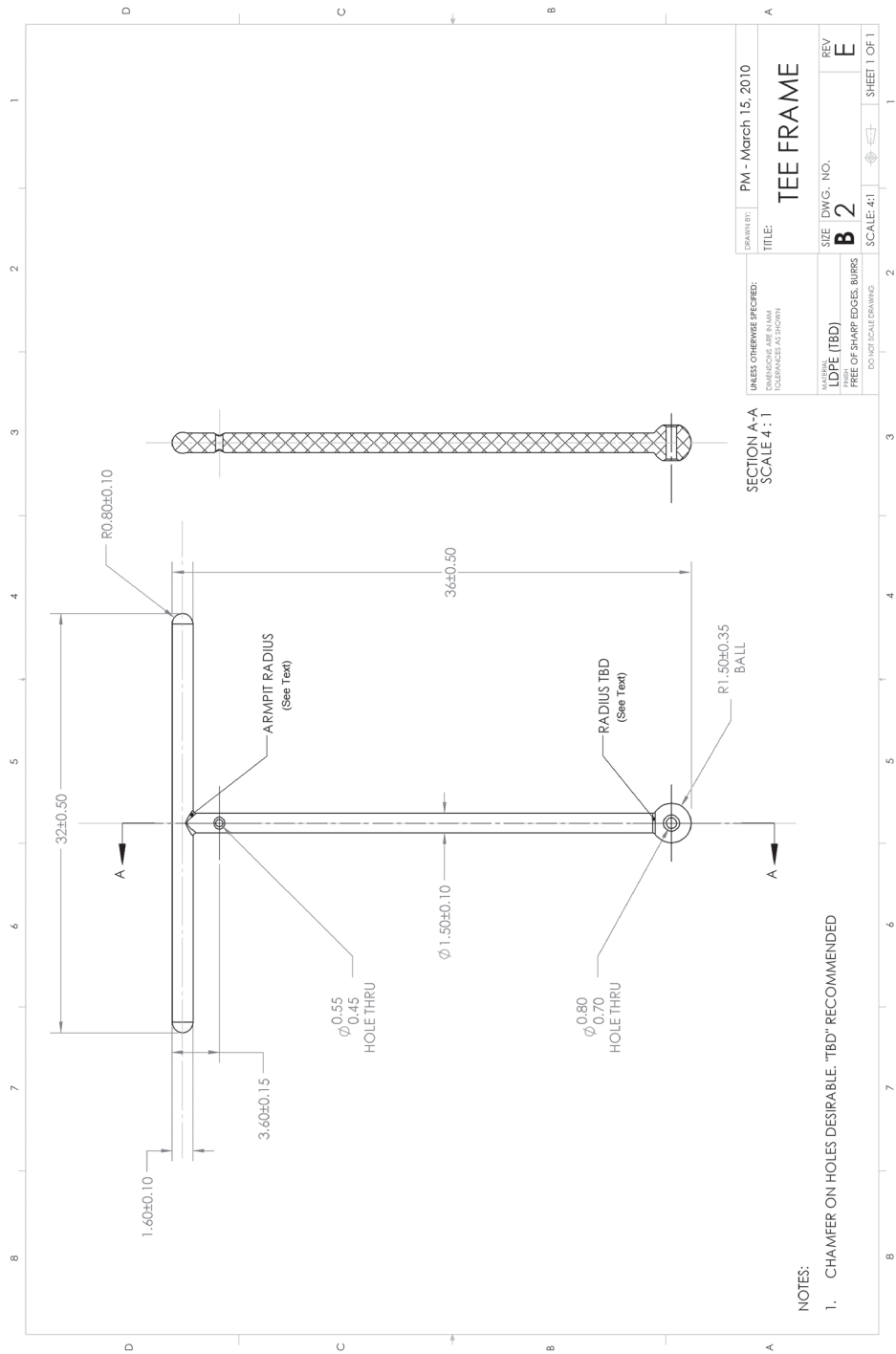
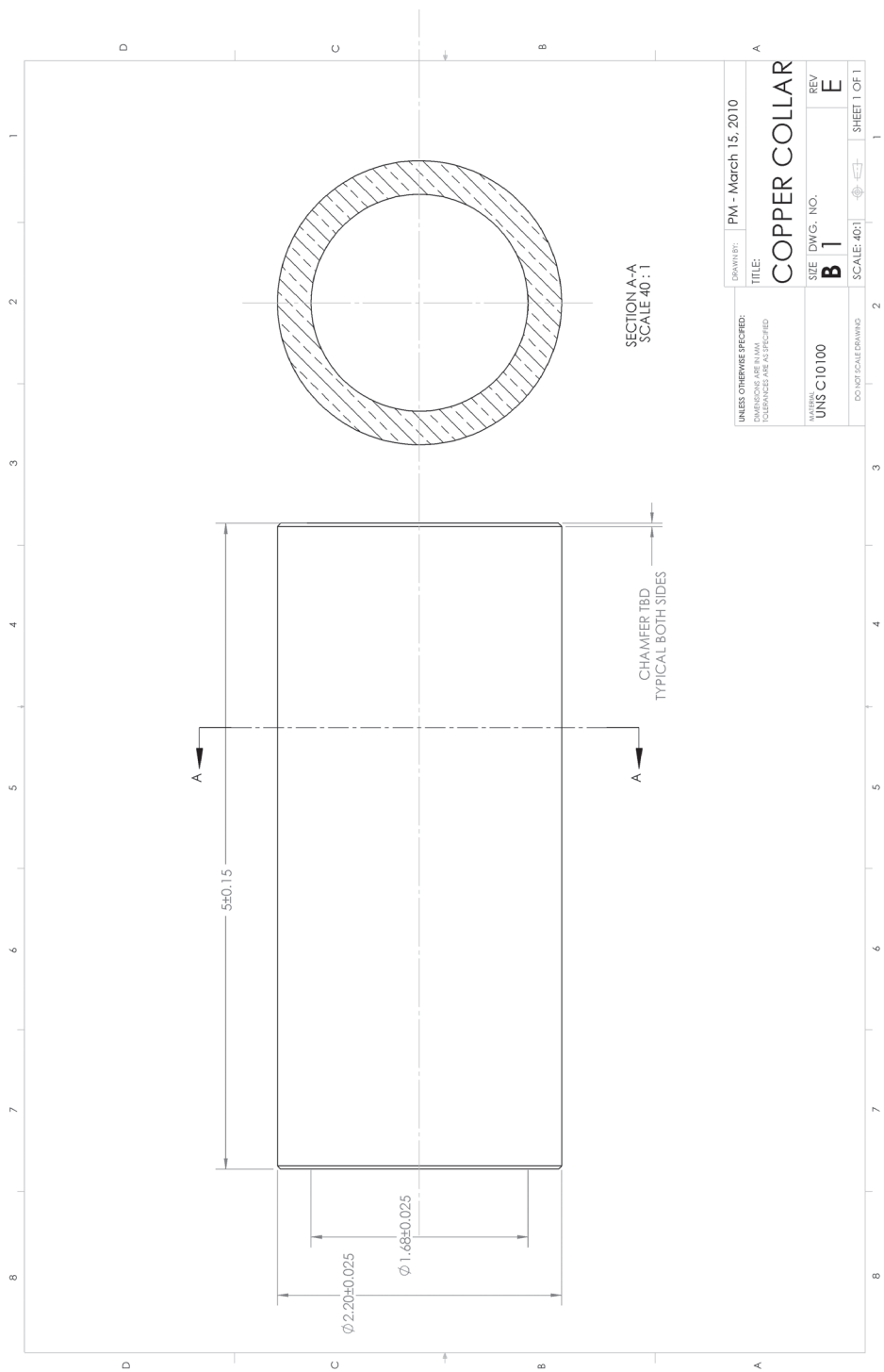
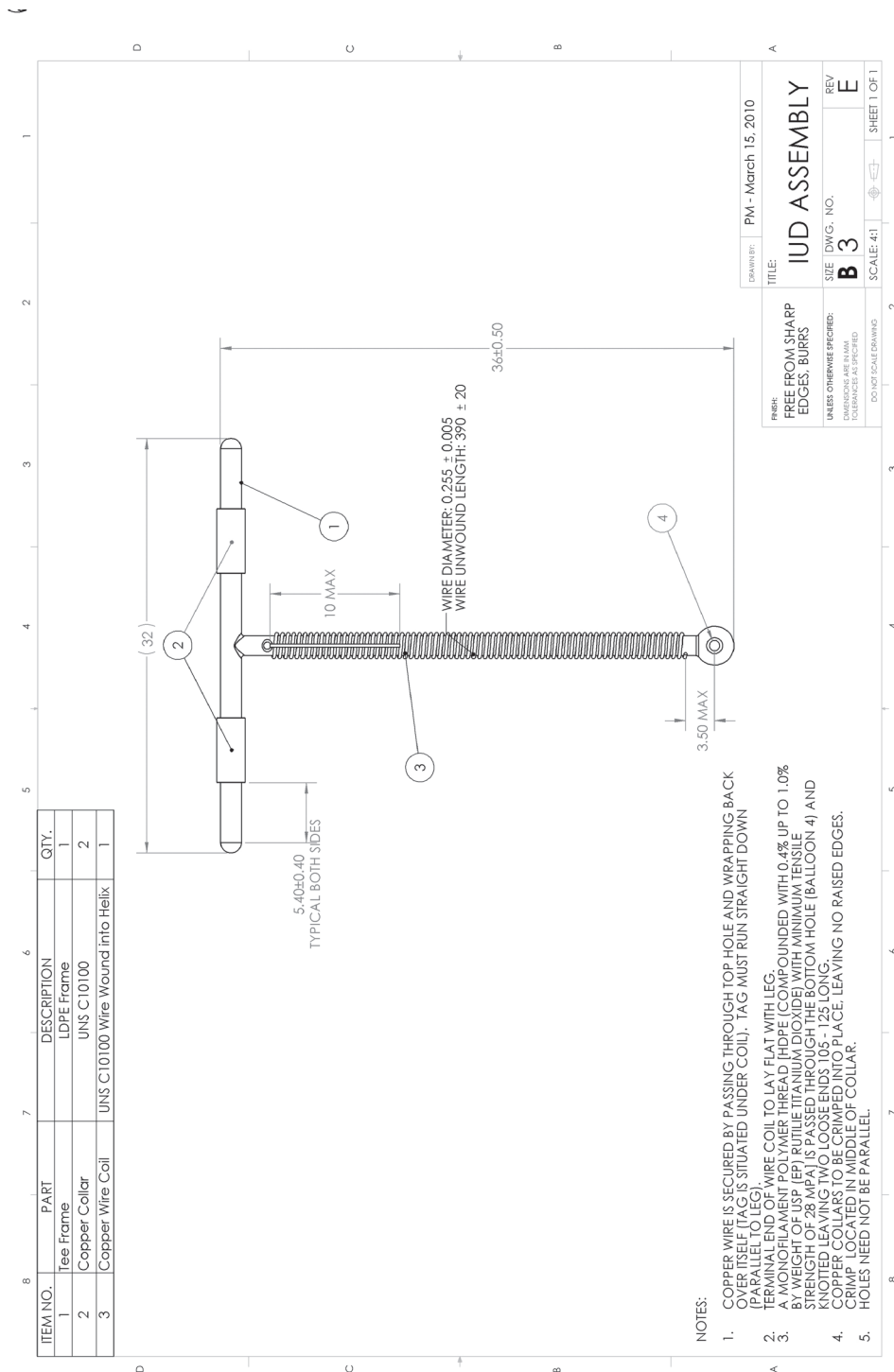


Figure 2. Copper collar—landscape



**Figure 3. IUD assembly—landscape**



An e-drawing is provided<sup>1</sup> at <http://tinyurl.com/395u6d2>. This e-drawing requires the download of a free viewer for Solidworks e-drawings from [http://www.solidworks.com/sw/support/eDrawings/e2\\_register.htm](http://www.solidworks.com/sw/support/eDrawings/e2_register.htm).

<sup>1</sup> The hyperlink reference shown as <http://tinyurl.com/395u6d2> is to the manufacturers' community virtual network on the WHO Implementing Best Practice (IBP) Knowledge Gateway and is accessible only by the manufacturers and UNFPA and WHO staff. Requests for access to this site must be sent to UNFPA Procurement Section, Copenhagen, Denmark, <http://www.unfpa.org/public/procurement>.



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