Annex 3

Procedure for assessing the acceptability, in principle, of TCu380A intrauterine devices for purchase by United Nations agencies

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1. **Introduction**

1.1 **Background**

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

The World Health Organization (WHO), the United Nations Population Fund (UNFPA) and other key partners developed an evidence-based list of Reproductive Health Essential Medicines (2005), which was subsequently approved by the WHO Expert Committee on Selection and Use of Essential Medicines. From this list and 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 Prequalification Programme, 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 intrauterine devices (IUDs) and male latex condoms and that the UNFPA scheme would be harmonized with that of the WHO Prequalification Programme.

WHO continues its normative work and together with key partners, WHO has recently supported the preparation of a Cochrane review\(^1\) on copper-bearing IUDs in order to provide an evidence-base to support the revision of the International Standard for IUDs, ISO 7439: 2002. A 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 IUD as the most appropriate device for bulk procurement by UNFPA. In addition, a detailed technical review process is currently being undertaken to update the bulk procurement specification for TCu380A IUDs. This will be published by July 2008. The current specification will be used until the revised specification has been published.

This document describes the implementation of the 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.

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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 conform to the international standard ISO 7439 and the TCu380A IUD specification and retain their effectiveness throughout their stated shelf-life.
- Broaden the supplier base for TCu380A IUDs, which 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 intrauterine devices

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. 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 EOI on behalf of a manufacturer who undertakes the process described above. The prequalification scheme does not apply to suppliers/agents engaged only with testing and re-packaging.

2.2 Expression of Interest

2.2.1 Calls for and submission of Expressions of Interest


The invitation is open and transparent and invites manufacturers and/or their agent as described in Section 2.1 above, to submit an EOI for the products listed in the invitation. The applicant/manufacturer should submit their EOI to the UNFPA focal point with the relevant information requested. The applicants/manufacturers will be given a specified period within which to submit their responses from the time of publication of the advertisement. The information must be submitted in English (see Section 2.10 Language).

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

WHO and UNFPA will provide further guidance on the submission of documentation for prequalification and make such guidance available on the WHO and UNFPA web sites.
In submitting an EOI for product evaluation, the applicant/manufacturer 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 for review; and
- a site master file, for each manufacturing site listed in the product dossier, in the requisite format specified in the WHO/UNFPA guidance documents for submitting a site master file.

The information must be accompanied by copies of all current certifications/accreditations, all manufacturing licences/registrations held, and a copy of the company registration.

The documentation should be submitted in English, and be sent by courier or registered mail (see Section 2.10 Language).

2.2.2 Assessment of documents submitted

The aim of the assessment of submitted documentation will be to determine whether the applicant/manufacturer meets the minimum requirements detailed in the relevant ISO standards\(^2\) and the TCu380A IUD specification\(^3\) in respect of product quality and safety, production and quality management, regulatory approvals and capacity of production.

2.2.2.1 Initial screening of documentation

UNFPA will aim to screen the documentation within 30 days of the closing date for receipt of 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. In the event of non-compliance, the dossier may be rejected on the grounds of incompleteness and returned to the applicant. Dossiers that are considered complete as the result of the administrative screening will be retained by UNFPA for evaluation purposes.

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

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\(^2\) ISO standards are available from: International Organization for Standardization, ISO Secretariat, 1 rue de Varembé, Case Postale 56, CH-1211 Geneva 20, Switzerland.

\(^3\) The TCu380A specification is available on the WHO (http://www.who.int/prequal/) and UNFPA (http://www.unfpa.org) web sites.
Assessment of the product dossier and the site master file

UNFPA aims to convene a group of experts acting as assessors to complete the assessment of the product dossier and the site master file within a specified time period (90 days) of the closing date for receipt of responses.

The submissions will be evaluated by assessors with 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 Sections 3 and 4 of this procedure.

The assessment of the submitted documentation will be done in accordance with SOPs established by 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 including results from previous site inspections and laboratory test results on products produced by the manufacturer, which may be in UNFPA's possession.

UNFPA aims to advise the applicants/manufacturers of the outcome of the assessment of documentation within 30 days after completion of the assessment. If the application is found to be in compliance with the requirements of UNFPA, as detailed on the WHO and UNFPA web sites, the manufacturing site will be scheduled for site inspection.

Site inspection

UNFPA will plan and coordinate inspections at the above-mentioned manufacturing sites to assess the manufacturing process and the product and quality management systems for compliance with general and performance requirements of the TCu380A IUD specification and good management practice including, in particular, the following international standards:


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 detailed knowledge of the processes for manufacturing IUDs, documented qualifications and experience in auditing and quality management systems; and have specific experience of inspecting IUD manufacturing sites. The inspectors must comply with the confidentiality and conflict of interest rules of UNFPA, as detailed in Sections 3 and 4 of this procedure. If needed, to ensure uniformity in inspection procedures UNFPA will provide training to these experts.

Where possible UNFPA will appoint at least one inspector able to communicate in 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. 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 identity of each inspector, the 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 proposed team composition. 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.

Each team will perform the inspections and report on its findings to UNFPA in accordance with the SOPs established by UNFPA for that purpose so as to ensure a standardized harmonized approach.
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 Sections 3 and 4 of this procedure.

2.3.2 Scope and scheduling

The applicant/manufacturer will be informed of the scope of the inspectors’ activities, prior to the inspection. The key components of the inspection are available on the WHO and UNFPA web sites under the heading: Scope of manufacturing site inspection: TCu380A IUDs. However, 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 as well as records and data that relate to the production of the IUDs. Where necessary manufacturers must organize access to the facilities of suppliers. 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 reasonable efforts to accommodate any requests made by the manufacturer and/or regulatory agencies to change the date 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 Section 2.5.

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 manufacturer 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 their 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 facilities, which are in any way involved in the production of the
product(s) concerned, and to 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 during the initial assessment procedure will lead to termination of the site inspection.

2.4 **Product testing**

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

The samples will be packed and sealed by the inspectors or the independent sampler, as may be appropriate. The inspectors may take the samples with them, or arrange for the manufacturer to have the sealed boxes sent to the selected laboratory by courier at UNFP A’s expense.

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 accredited test laboratories selected by UNFP A. 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 applicant.

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

At the conclusion of the inspection, the inspectors will provide 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 UNFP A with a copy to the manufacturer.

In addition, the inspection team will finalize its main report according to the established UNFP A SOP and format, describing the findings, evidence and recommendations, as described on the WHO and UNFP A web sites under the heading: *Scope of manufacturing site inspection: TCu380A IUDs*. The report will be submitted to UNFP A.

The inspection report will be communicated by UNFP A to the applicant/manufacturer. If any additional information is required, or corrective action has to be taken by the manufacturer, UNFP A will postpone its decision on the acceptability of the site(s), until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.
UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the applicant/manufacturer is either not able to provide the required information or to implement the corrective actions within 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 will be entitled to use and publish such reports, subject always, however, to the protection of any commercially confidential information of the applicant/manufacturer(s).

Confidential information may include:

— confidential intellectual property, “know-how” and trade secrets (including, e.g. formulas, programmes, process or information contained or embodied in a product, unpublished aspects of trademarks and patents); and
— 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/manufacturer.

Notwithstanding the foregoing, UNFPA and WHO reserve the right to share 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 manufacturer, in consultation with the assessors and inspectors and will make a final decision about the outcome of the prequalification process.

Based on this assessment UNFPA will either:

• Prequalify the TCu380A IUD manufacturing site without conditions. This will only be the case when there is no evidence that corrective action should be submitted to UNFPA.

Or
• Require the manufacturers, where deemed necessary, to undertake specified corrective action(s). The manufacturer must do this within an agreed period of time 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/manufacturer from resubmitting an application in response to future invitations for EOIs.

Where the inspectors recommended corrective action requiring a subsequent inspection, the manufacturer 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 Sections 2.3, 2.4, 2.5 and 2.6.

UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the applicant/manufacturer is not able to provide the required information or implement the corrective actions within a specified time period, 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 such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified international standards, detailed in the Appendix. If the applicant/manufacturer has not submitted a satisfactory response within 12 months of submission of the report to UNFPA, the application will lapse and the applicant/manufacturer will need to reapply in response to a future invitation for an EOI.

UNFPA aims to inform the manufacturer of the results of the process within 30 days of receipt of all final reports.
2.7 Listing of prequalified TCu380A intrauterine devices and manufacturing sites

Once UNFPA is satisfied that the quality assessment process is complete, and where the product dossier 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 WHO and UNFPA prequalification web sites. 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.

Each applicant will receive a letter from UNFPA informing them of the outcome of the quality assessment process.

2.8 Maintenance of the prequalification status

Once the product is included in the list of prequalified TCu380A IUDs and corresponding manufacturing sites, the applicant/manufacturer will be required to provide UNFPA with prior notification of any intended changes in the manufacturing site and/or the manufacturing process.

All manufacturers of prequalified TCu380A IUDs are required to advise UNFPA, four weeks prior to implementation, of any matter that affects the information on which the approval was based. This includes, 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 (referring to relevant parts of the dossier) to prove that the implementation of any intended variation will not have an 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. Compliance with
the requirement to report changes will be checked during the inspections carried out by UNFPA.

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 an independent test laboratory, selected by UNFPA, of defined and documented accreditation to the current ISO 17025 international standard. In the event of failure 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 to the applicant/manufacturer, including recommendations for action. UNFPA will require evidence of effective action taken, where relevant. UNFPA will make the report available to the applicant/manufacturer and to the appropriate authorities of the country where the manufacturing site is located, subject always to considerations of commercially confidential information, as referred to in Section 2.5 above.

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 WHO.

2.9 Reassessment

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 IUDs supplied by the manufacturer are considered by UNFPA, or one or more of the 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 the UNFPA or one or more of the United Nations agencies or organizations.
• If there is a significant change in one or more of the items listed in 2.8 above.

All relevant information including the reassessment of submitted documentation and the site inspection reports together with monitoring information will be considered by the designated UNFPA official and a decision will be made either 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, a further product testing and/or site inspection;

or

— suspend prequalified status.

UNFPA aims to advise the applicant/manufacturer 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 based. 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 the information submitted is subsequently found to be incorrect or fraudulent.

2.10 **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 should be in English. All reports issued by the assessors, inspectors and by UNFPA on the assessment and inspections 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.

2.11 **Fees**

At present, 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 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.

2.12 **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 out 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; and
- 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, at the manufacturer’s request, 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 proposed team composition 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.
Appendix

List of standards and specifications


