

OVERVIEW OF THE PREQUALIFICATION OF MALE CIRCUMCISION DEVICES ASSESSMENT PROCESS

Prequalification of Male Circumcision Devices

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1. Introduction

The World Health Organization (WHO) Prequalification of Male Circumcision Devices Programme is coordinated through the Diagnostics and Laboratory Technology Team (DLT), in the department of Essential Health Technologies (EHT). The aim of the WHO Prequalification of Male Circumcision Devices Programme is to promote and facilitate access to safe, appropriate and affordable Male Circumcision Devices of good quality in an equitable manner. Focus is placed on Male Circumcision Devices for their potential to accelerate delivery of male circumcision programmes in high HIV incidence settings and thus reduce risk of HIV infection in adult male populations.

The WHO Prequalification of Male Circumcision Devices Programme undertakes a comprehensive assessment of the submitted products through a standardized procedure which is based on WHO prequalification requirements. The prequalification of Male Circumcision Devices process includes three main components:

- review of the application form;
- review of the product dossier, including review of clinical evidence; and
- inspection of the manufacturing site(s).

Another element of the WHO Prequalification of Male Circumcision Devices Programme is the strengthening of the regulatory capacity of WHO Member States to improve pre- and post-market regulatory oversight of Male Circumcision Devices.

The findings of the WHO Prequalification of Male Circumcision Devices Programme are used to provide technical information principally to other United Nations (UN) agencies, but also to WHO Member States and other interested organizations, on particular Male Circumcision Devices.

Prequalification does not imply any approval by WHO of the Male Circumcision Devices and manufacturing site(s) in question (which is the sole prerogative of national regulatory authorities). Moreover, prequalification does not constitute any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety and/or performance.

2. Intended Audience

This document has been prepared to provide an overview of the WHO prequalification of Male Circumcision Devices process for manufacturers who seek an assessment of their product(s). It is recommended that manufacturers of Male Circumcision Devices wishing to apply for WHO prequalification of their product(s) read this document before starting the prequalification application process. This will ensure that they are aware of and prepared for all stages of the prequalification assessment process.

3. Process Overview

3.1. About prequalification of Male Circumcision Devices

The main goal of the WHO Prequalification of Male Circumcision Devices Programme is to improve access to Male Circumcision Devices that are safe, affordable, of good quality and are appropriate for use on adult male populations in resource-limited settings. To this end, the WHO

Prequalification of Male Circumcision Devices Programme provides information on the outcomes of the intermediate and final steps of the prequalification assessment process to UN agencies, WHO Member States, and other interested organizations to guide their procurement decisions.

Once a product has been prequalified, it is included in the WHO list of prequalified Male Circumcision Devices and becomes eligible to be invited into the procurement processes of UN agencies. Countries and other interested organizations also use the list of prequalified products as a tool for guiding their procurement decisions. Hence, prequalification of Male Circumcision Devices is a procurement-driven programme that aims to ensure cost-effective use of resources.

3.2. Eligibility for prequalification of Male Circumcision Devices

Applications for WHO prequalification of Male Circumcision Devices are only accepted from the manufacturer of the product.

The WHO Prequalification of Male Circumcision Devices Programme uses the Global Harmonization Task Force (GHTF) definition of a manufacturer:

***Manufacturer** means any natural or legal person with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use, under his/her name; whether or not such a medical device is designed and/or manufactured by that person himself or on his behalf by another person(s).¹*

3.3. "Re-branding" arrangements

WHO is aware that certain companies purchase finalized products from other manufacturers and then "re-brand" these products.

WHO considers a "re-branded" product to be one that is manufactured under identical conditions at the same manufacturing site(s) as the original product. In other words, a "re-branded" product is identical in every aspect to the product manufactured by the original manufacturer, except that the product is labeled with a "re-branded" product name and identifier.

WHO encourages joint applications by original manufacturers and "re-branders". Prequalification of Male Circumcision Devices applications for "re-branded" products will be considered based on the prioritization criteria.

A condition for the prequalification assessment of a "re-branded" product is that the original product manufacturer and the "re-brander" explicitly consent to the public disclosure by WHO of this "re-branding" arrangement.

3.4. Prioritization criteria for the review of applications

In order to meet the needs of WHO Member States and UN agencies, conditions for prioritization of the review of applications for prequalification of Male Circumcision Devices have been established, which take into account a number of aspects such as:

¹ This definition for manufacturer is based on definitions used by the Global Harmonization Task Force (GHTF). The GHTF is a voluntary group of representatives from national medical device regulatory authorities and the regulated industry and was formed to encourage convergence in regulatory practices. This internationally accepted approach of defining a manufacturer has been adopted to ensure that there is a clear understanding of the term "manufacturer" across international markets. For further details visit the following website: <http://www.ghtf.org/documents/>

- the need for male circumcision devices for adult male populations ;
- the appropriateness of the product for use in resource-limited settings;
- the requests from WHO Member States for particular male circumcision devices;
- the performance capabilities of particular male circumcision devices; and/or
- the availability of currently prequalified products that are similar or the same.

Although all applications received from manufacturers will be reviewed in accordance with this procedure, those products meeting the prioritization criteria will be given priority. The prioritization criteria are periodically reviewed and made publicly available by WHO. This is done in consultation with other UN agencies and with relevant experts WHO also obtains input from WHO Member States to determine which male circumcision devices are of priority to them.

3.5. Readiness for prequalification

To ensure that WHO can prequalify Male Circumcision Devices as efficiently as possible, it is expected that manufacturers will be fully prepared for prequalification before submitting the product dossier.

WHO reserves the right to terminate the prequalification assessment process at any time/stage if the manufacturer is not able to, or fails to, provide the required information, and/or the manufacturer is unable to implement any corrective actions which WHO may require in a specified time period, or when the information supplied is inadequate for effective prequalification assessment. In this case, the manufacturer will not be eligible to re-apply for WHO prequalification assessment for one year from the date of the notification of termination.

3.6. Components of the prequalification of Male Circumcision Devices assessment process

The prequalification of Male Circumcision Devices process includes three main components:

- review of an application form and product dossier
- review of clinical evidence
- inspection of the manufacturing site(s).

Figure 1 depicts the way in which the prequalification of Male Circumcision Devices process proceeds through the particular assessment stages.

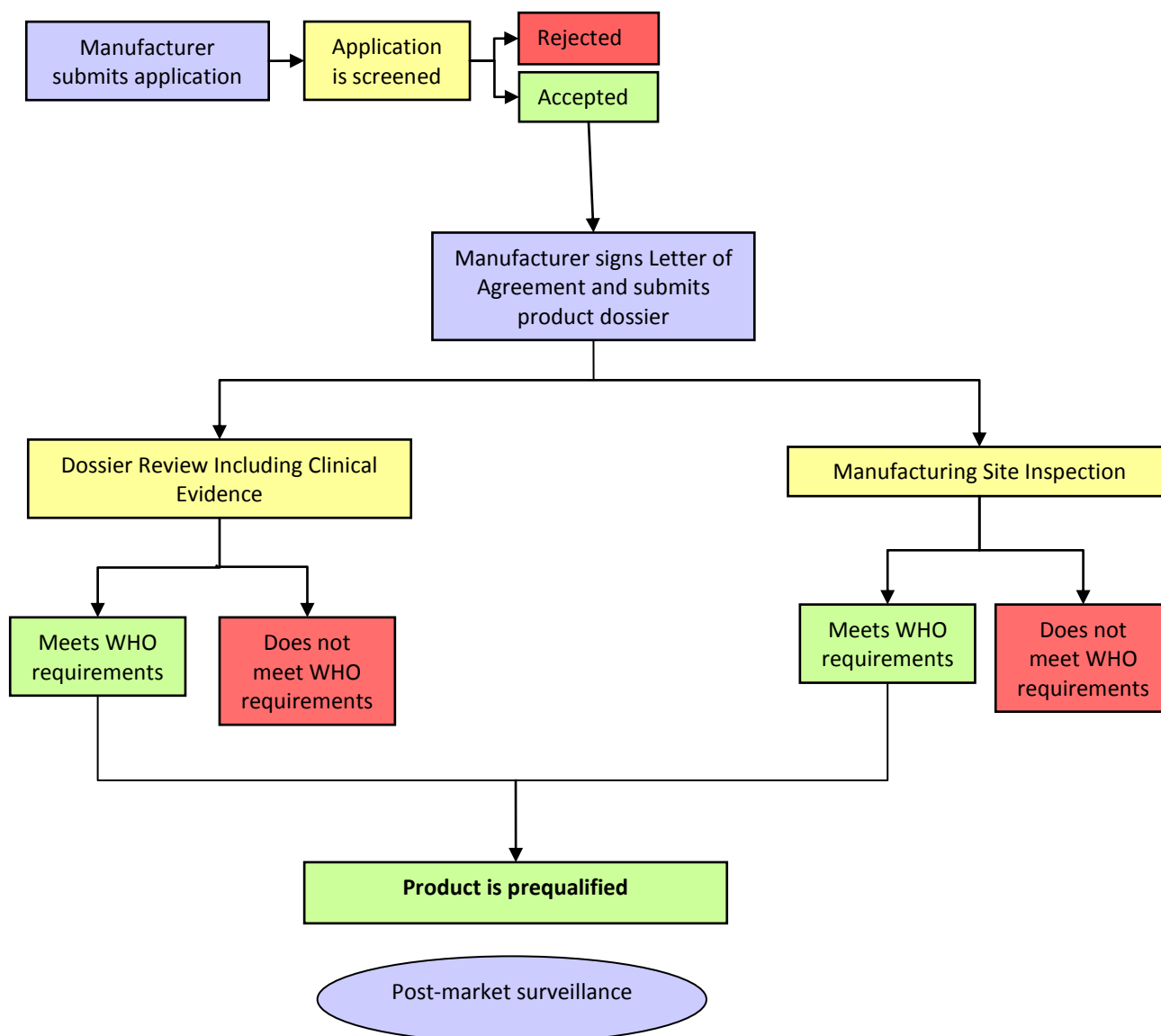


Figure 1: Overview of the prequalification of Male Circumcision Devices process

WHO recognizes the assessment of relevant products by national regulatory authorities which apply stringent standards for quality, similar to those applied by WHO. Provided that the national regulatory authorities and holders of the regulatory approvals of male circumcision devices submitted for WHO prequalification are willing to share certain information with WHO on the product(s) in question, WHO may consider in the WHO prequalification assessment process all or part of the findings of the scientific assessment and inspections conducted by the regulatory authority concerned.

4. Review of the Application Form and Product Dossier

4.1. Application form submission

Submission of the completed application form is the first step in the prequalification assessment process. This completed application form provides summary information about the product and the manufacturer.

The manufacturer should complete the application form and provide all requested information as prescribed by the document "Instructions for the Completion of the Application Form".

4.2 Application form review

WHO reviews the application form to determine whether it is complete (applications that are incomplete will not be considered) and whether the manufacturer uses a quality management system with respect to the submitted product. If that is the case, the manufacturer is notified that the product is ready to proceed further in the assessment process² and a formal Letter of Agreement is subsequently sent to him by WHO. The Letter of Agreement is to be duly signed and sent back to WHO before the process can proceed further. There will be exceptionally no prequalification fee levied for the assessment of Male circumcision devices. Upon completion of these requirements, the manufacturer will receive an invitation to submit a product dossier.

4.3 Product dossier submission

The male circumcision device will only proceed to the product dossier review stage if and when WHO formally invites the manufacturer to submit a product dossier. The manufacturer should compile and submit the product dossier as prescribed by the document "Instructions for Compilation of a Product Dossier". Furthermore, the product dossier should be submitted using the document "Product Dossier Checklist" as the first page. All sections of the dossier should be cross-referenced to this first page. The content of the product dossier should be consistent with the information submitted in the application form.

4.4 Product dossier review

Once the product dossier has been received by WHO, it is screened for completeness and provided it contains all the required information, it undergoes a full review. If the product dossier is incomplete, the manufacturer will be informed that an incomplete product dossier has been received and will be requested to complete it within a specified time period. In the event of non-compliance, the product dossier will be rejected on grounds of incompleteness and the prequalification process will be terminated.

The information submitted in the product dossier will be reviewed by WHO staff and external experts (assessors) appointed by WHO. They will also review clinical evidence that WHO may obtain directly from principal investigators conducting independent clinical trials on the male circumcision device in the intended use settings.

The product dossier should contain clinical evidence that demonstrates conformity of the device with the Essential Principles³ that apply to it. Clinical evidence is an important component of the technical documentation of a male circumcision device for use in public health male circumcision programmes for HIV prevention, which along with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity to the Essential Principles.

A clinical study (also called clinical investigation or clinical trial) is a systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance

² As mentioned under section 3.4 above, those products meeting one or more of the prioritization criteria will be given priority.

³ The Essential Principles of Safety and Performance of Medical Devices include essential safety and performance criteria for a medical device that allow the manufacturer to demonstrate that the product is suitable for its intended use. For further information see the below link:
<http://www.ghtf.org/documents/sg1/sg1n41r92005.pdf>

of a male circumcision device. The undertaking of a clinical study is a scientific process that represents one method of generating clinical data.

The objective of a clinical investigation is to assess the safety and performance/efficacy of the device in question and evaluate whether the device is suitable for the purpose(s) and the population(s) for which it is intended.⁴

Data from at least one randomized controlled trial that compares the performance of the device with standard procedures (currently surgical), and at least one non-comparative field study in settings of intended use will be required for review.

The assessors will act as temporary advisers to WHO. They must have the qualifications and experience in the relevant fields and must comply with the confidentiality and conflict of interests rules of WHO. The assessment of product dossiers will be done in accordance with an SOP established by WHO for that purpose so as to ensure uniformity in the conducted review and timeliness of assessment activities.

In the event that a male circumcision device has received a recent valid regulatory approval from a stringent regulatory authority and both the holder and provider of the approval are willing to share certain information related to the approval with WHO, a fast track assessment procedure, as defined in a specific SOP established by WHO, may be applied.

The findings from the product dossier assessment shall be communicated in writing to the applicant.

The decision by WHO to continue the prequalification assessment process is based on the successful review of the product dossier content. Acceptable dossiers will proceed to the manufacturing site(s) inspection stage.

NOTE: Manufacturers should not submit a product dossier unless instructed to do so by WHO. The product dossier will otherwise be returned to the manufacturer without review.

5. Inspection of the Manufacturing Site(s)

Inspection of the manufacturing site(s) will occur following a successful review of the product dossier. Inspections are carried out to assess the adequacy and effectiveness of the manufacturer's quality management system and the correct implementation of documented procedures.

The inspection of the manufacturing site(s) is conducted to assess compliance with the quality management standard *ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes* and with other relevant international standards and Global Harmonization Task Force (GHTF) guidelines.

The manufacturer will be contacted by the WHO officer in charge of coordinating the inspection team to organize the practical arrangements for the inspection. The inspection team is composed of WHO staff and external experts (inspectors) appointed by WHO. The inspectors will act as

⁴ ISO 14155-1:2003
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temporary advisers to WHO. The inspectors must have the relevant qualifications and experience to perform such inspections. Furthermore, they must comply with the confidentiality and conflict of interest rules of WHO. The manufacturer will be informed of the identity of the proposed inspectors prior to the site inspection and receive their curriculum vitae. The manufacturer has the opportunity to express concerns to WHO regarding any of the inspectors before the visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer may officially object (in writing) to a team member's participation in the site visit within 10 days of receipt of the proposed inspection team composition. Representatives of the national regulatory authorities may accompany the inspection team to the manufacturing site(s) as observers.

In general, the inspection will take three to five working days. Each team will perform the inspection and report on its findings to WHO in accordance with SOPs established by WHO for that purpose, so as to ensure a standard harmonized approach. A preliminary report detailing non conformances (if any) will be provided on the final day of the inspection. An inspection report will be issued approximately one month after the inspection. If any additional information is required, or corrective action has to be taken by the manufacturer, WHO will postpone its decision on the acceptability of the sites(s) concerned until such information has been validated or the corrective action(s) have been taken and found satisfactory in light of the specified requirements. Re-inspection may occur, when required, to confirm the corrective actions and/or to ensure ongoing compliance. A summary of the final inspection report will be published on the WHO website.

6. Outcome of the Prequalification Assessment

Once WHO is satisfied that the prequalification assessment of a product is complete and the overall findings demonstrate that the product meets all WHO prequalification requirements, the product, as manufactured at the specific manufacturing site(s), shall be included in the WHO list of prequalified Male Circumcision Devices. The list of prequalified Male Circumcision Devices will be compiled in accordance with a procedure established by WHO for final decision-making on inclusion in the list. The list will be published on the WHO website and will specify the prequalification (PQ) number, the name(s) of the prequalified male circumcision device, the name(s) of the manufacturer(s) and the product (catalogue) number(s). These products are then eligible for participating in the UN agencies procurement processes.

The manufacturer shall receive a letter from WHO informing him of the outcome of the overall assessment of the product. Once the product is included in the WHO list of prequalified Male Circumcision Devices, the manufacturer shall be responsible for keeping WHO updated on all relevant aspects of the product, its manufacture and control.

The decision to list a male circumcision device is made based upon information available to WHO at the time of the prequalification assessment including product dossier review, review of the clinical evidence and manufacturing site inspection(s) conducted by WHO. This decision is subject to change on the basis of new information that may become available to WHO. If there is evidence of serious safety and/or quality issues in relation to a prequalified product, WHO may delist the product until results of further investigations become available and are assessed by WHO.

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

Manufacturers should understand that it is not WHO's mandate to issue approvals, certificates or licenses for Male Circumcision Devices. This responsibility lies with the regulatory authority of each country. Furthermore, WHO does not, as a matter of policy, endorse any specific commercial product over others. In addition, in keeping with WHO policy, the results of the prequalification assessment, the participation in the WHO prequalification process, the inclusion in the WHO list of prequalified Male Circumcision Devices or the WHO name and emblem, should not be used by the manufacturers or any other party for commercial and/or promotional purposes. WHO will not accept any liability or responsibility whatsoever for an injury, death, loss, damage or other prejudice of any kind that may arise as a result of, or in connection with the procurement, distribution and use of any product, as to which WHO has published the assessment results and/or which is included in the WHO list of prequalified Male Circumcision Devices.

As WHO is responsible for the prequalification procedure, the ownership of the reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any commercially sensitive confidential information of the manufacturer. "Confidential information" in this context means:

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

Subject always to the protection of commercially sensitive confidential information, WHO will in particular make publicly available the following information throughout the prequalification process (manufacturers should note that WHO shall also be entitled to publish negative assessment outcomes):

- the names of products and manufacturers that have applied for prequalification of Male Circumcision Devices and their prequalification status;
- a brief report on the findings from the dossier review;
- the findings of the review of the clinical evidence relating to the product; and
- a summary report of the findings from the inspection of the manufacturing site(s).

Notwithstanding the foregoing, WHO reserves the right to share the full assessment and inspection reports with UN agencies and the relevant authorities of interested WHO Member States.

7. Post-Market Surveillance of WHO Prequalified Male Circumcision Devices

A post-market surveillance system has been developed by WHO aiming to ensure the ongoing compliance of prequalified Male Circumcision Devices with prequalification requirements. The WHO post-market surveillance system includes collection of information on quality, safety or performance of the male circumcision device after it has been prequalified and placed on the market as well as notification and evaluation of vigilance events enabling appropriate action to be taken by national regulatory authorities⁵ or WHO.

⁵ The WHO post-market surveillance system is not geared to interfere with national regulatory authorities post-market surveillance requirements.

As soon as a male circumcision device is accepted into the prequalification assessment process, and as long as such male circumcision device is on WHO's list of prequalified Male Circumcision Devices, the manufacturer should agree to undertake the following post-market surveillance activities:

- To notify WHO of all adverse events relating to this product that have affected (or could have affected) the performance of the product, safety of the users of this product or safety of any person associated with this product. WHO may request that the manufacturer provides further information relating to the event, including details regarding the preventive and correction actions taken;
- To notify WHO of all events which require field safety corrective actions such as withdrawal of products from sale or distribution, physical return of the product to the manufacturer, product exchange, destruction of the product, product modification/s or additional advice provision to customers to ensure that the product continues to function as intended; and
- If required, to supply sufficient quantities of the prequalified product to WHO, or laboratories designated by WHO, free-of-charge and delivered duty paid, for post-market surveillance testing.

Adverse events/complaints concerning a prequalified male circumcision device communicated to WHO will be investigated in accordance with a SOP established by WHO for that purpose. Depending on the nature of the event/complaint, WHO may notify the manufacturer of the event/complaint, and/or may notify national regulatory authorities in the country/region where the product is manufactured and/or supplied. Subject always to the protection of commercially sensitive information as referred to above, WHO shall be entitled to make such reports public. In addition, WHO reserves the right to share the full vigilance report with the relevant authorities of interested Member States of the Organization and interested UN agencies.

8. No Prequalification Assessment Fee

The non-refundable prequalification assessment fee of US \$12,000.- will be exceptionally waived for the assessment of male circumcision devices.

9. Eligibility to Participate in WHO and other UN Procurement Processes

The WHO prequalification assessment process is independent from WHO's and other UN agencies' procurement processes. WHO prequalification of a male circumcision device is a prerequisite for such male circumcision devices to be considered eligible for participation in WHO's and other UN agencies' procurement processes⁴. However, it does not imply that such male circumcision device will actually be procured by WHO or other UN agencies, as additional procurement criteria apply.

⁴ Prequalification of Male Circumcision Devices will become mandatory after expiry of the transitional period enabling processing of prequalification applications.

10. Notification of Variations to Prequalified Male Circumcision Devices

WHO prequalifies a male circumcision device as it is submitted to and assessed by WHO at a particular point in time. If any changes/variations are made to the product, manufacturing site(s) or manufacturing processes, the male circumcision device may no longer be considered as prequalified. Therefore, the manufacturer should inform WHO of any changes/variations by submitting a prequalification variation notification. WHO shall review this change/variation notification in accordance with an established SOP to determine if the change/variation:

- can be accepted based on the information provided by the manufacturer
- requires a prequalification variation assessment
- is so substantial that the product resulting from the change/variation should be considered as a new product.

The manufacturer will be advised of the outcome of the variation notification review and will be instructed on how to proceed.

11. Validity of Prequalification Status

WHO will arrange for the products and manufacturing sites included in the WHO list of prequalified Male Circumcision Devices to be reassessed at regular intervals. If, as a result of this reassessment, it is found that a product and/or specified manufacturing site no longer complies with the WHO requirements, such products and manufacturing sites will be removed from the list. Failure of a manufacturer to participate in the reassessment procedure will also lead to removal from the list.

12. Confidentiality

The assessors and inspectors will treat all information to which they will gain access during the assessments and inspections, or otherwise in connection with the discharge of their responsibilities in regard to this procedure, as confidential and proprietary to WHO or parties collaborating with WHO 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 purpose other than the assessment/inspection activities described in this document; and
- 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 WHO (including the manufacturers); or

- was in the public domain at the time of disclosure by or on behalf of WHO (including the 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.

13. Conflict of Interest

Prior to formalizing arrangements with inspectors and assessors, WHO will also (in addition to the above-mentioned confidentiality undertaking) require each of them to complete and sign the WHO Declaration of Interests form.

If, based on the above mentioned Declarations 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), the aforesaid experts will discharge their functions exclusively as advisers to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed is correct and complete, and that he/she will immediately notify WHO of any change in this information.

14. Relevant Documents

14.1. Documents relevant to the application form / product dossier review

The following documents provide information to guide the manufacturer through the requirements of the application /product dossier stages:

- Instructions for Completion of the Application Form: Document PQMC_017
- Application Form: Document PQMC_015
- Instructions for Compilation of a Product Dossier: Document PQMC_018
- Product Dossier Checklist : Document PQMC_049.

14.2. Documents relevant to the inspection of the manufacturing site(s) stage

The following documents provide information to guide the manufacturer through the requirements of this prequalification stage:

- Information for Manufacturers on Prequalification Inspection Procedures for the Sites of Manufacture of Male Circumcision Devices - Document PQMC_014
- ISO 13485:2003 Medical devices - Quality management systems - Requirements for regulatory purposes.
- ISO/TR 14969 Medical devices - Quality management systems - Guidance on the application of ISO 13485.

15. Contact Information

Any inquiries regarding the prequalification of Male Circumcision Devices should be addressed to: diagnostics@who.int