OVERVIEW OF THE WHO PREQUALIFICATION OF MALE CIRCUMCISIION DEVICES ASSESSMENT

WHO Prequalification of Male Circumcision Devices
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1. Introduction

World Health Organization (WHO) prequalification of male circumcision devices (MCDs) is coordinated through the department of Essential Medicines and Health Products. Focus is placed on Male Circumcision Devices for their potential to accelerate delivery of male circumcision programmes in high HIV incidence settings and, thereby, contribute to reducing the risk of HIV infection in adult male populations.

WHO prequalification of Male Circumcision Devices is a comprehensive quality assessment of individual MCDs through a standardized procedure aimed at determining whether the product meets WHO prequalification requirements.

The prequalification assessment process for MCDs includes the following components:

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

Products submitted for prequalification assessment that meet, as determined by WHO, the WHO prequalification requirements are included in the WHO list of prequalified MCDs. The duration of the validity of the prequalification status of a product is dependent on the manufacturer’s fulfilment, within the applicable deadlines, of its post-qualification obligations and requirements, including:

- prequalification commitments;
- annual reporting;
- reporting of changes;
- post-market surveillance obligations;
- receiving re-inspections; and
- ongoing compliance with WHO prequalification technical specifications, as applicable.

The findings of WHO prequalification\(^1\) are used to assess the safety, quality and performance of commercially available MCDs for the purpose of providing guidance to interested United Nations (UN) agencies and WHO Member States in their procurement decisions.

2. Intended audience

This document has been prepared to provide manufacturers with an overview of the WHO process for prequalification assessment of MCDs (the prequalification assessment process). Manufacturers wishing to apply for WHO prequalification of their product(s) should read this document before applying, so that they can be aware of and prepared for all stages of the prequalification assessment process.

\(^1\) Prequalification does not imply any approval by WHO of the product and manufacturing site(s). Moreover, prequalification does not constitute any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety, quality or performance.
3. Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Dossier screening</td>
<td>Systematic process to ensure that all requisite sections of the product dossier are submitted</td>
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<tr>
<td>Dossier review</td>
<td>Review and assessment of documentation including data, protocols, reports, procedures, etc., to support the quality, safety and performance of a product for the purpose of WHO prequalification.</td>
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<tr>
<td>Inspection of manufacturing site(s)</td>
<td>Inspection of the manufacturing site(s) of product undergoing prequalification assessment</td>
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<tr>
<td>Labelling review</td>
<td>Review and assessment of the instructions for use and product labels</td>
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<td>Manufacturer</td>
<td>Any natural or legal person with responsibility for design and/or manufacture of an MCD with the intention of making the MCD available for use, under his or her name, whether or not such an MCD is designed and/or manufactured by that person him- or herself or on his or her behalf by (an)other person(s).</td>
</tr>
<tr>
<td>Rebranded product</td>
<td>A rebranded product is identical in every respect to the product manufactured by the original manufacturer, except that the product is labelled with the &quot;rebranded&quot; product name and product code, and bears the rebrander’s name.</td>
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<tr>
<td>Rebrander</td>
<td>A manufacturer of a rebranded MCD.</td>
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<tr>
<td>Regulatory version</td>
<td>Relates to the information associated with a submission for approval by a regulatory authority. The submitted version is defined by all of the documentation related to development, manufacture and intended use, labelling and post-market surveillance of the product and all the documented evidence supporting the safety and performance claims associated with that submission. If any aspect of this documentation differs in any way between the submissions to different regulatory authorities or assessment bodies (United States Food and Drug Administration, Health Canada, a Notified Body for CE marking, etc.) it is considered to be a different regulatory version.</td>
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4. Abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>GHTF</td>
<td>Global Harmonization Task Force</td>
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<td>IMDRF</td>
<td>International Medical Device Regulators Forum</td>
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<tr>
<td>IFU</td>
<td>instructions for use</td>
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<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
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<tr>
<td>MCD</td>
<td>male circumcision device</td>
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5. About prequalification of MCDs and procurement

The goal of the WHO prequalification of MCDs is to assess the safety, quality and performance of commercially available MCDs for the purpose of providing guidance to interested UN agencies, WHO Member States in their procurement decisions.

Once a product has been prequalified, it is included in the WHO list of prequalified MCDs and becomes eligible to participate in the procurement processes of UN agencies. WHO Member States are encouraged to use the WHO list of prequalified MCDs for their respective procurement decisions. Nevertheless, UN agencies and WHO Member States using information from the WHO prequalification of MCDs process should perform additional steps of qualification prior to purchasing products included in this list including steps such as ensuring the supplier’s financing stability and standing, the ability to supply the required quantities of the product, security of the supply chain, quality control testing, and other relevant aspects.

6. Eligibility for prequalification of MCDs

6.1. Original manufacturer

Applications for WHO prequalification of MCDs are accepted only from the legal manufacturer of the product.²

6.2. Rebranded products

WHO is aware that several manufacturers purchase finalized products from other companies, and then "rebrand" and place these products on the market under their own name or brand. Such products are also known as original equipment manufacturer (OEM) products.

WHO considers a rebranded product to be one that is manufactured under identical conditions at the same manufacturing site(s) as the original product. In other words, a rebranded product is identical in every respect (including the intended use) to the product manufactured by the original manufacturer, except that the product is labelled with the rebranded product name and product code, and bears the rebrander’s name or brand.

Rebranded products are outside the scope of the WHO prequalification of MCDs process, and hence are not accepted for prequalification assessment.

6.3. Commercial availability

Applications for WHO prequalification of MCDs are only accepted for products that are commercially available at the time of submission for prequalification assessment.

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² The definition of a manufacturer is based on the definition used by the Global Harmonization Task Force (GHTF), and later adopted by International Medical Device Regulators Forum (IMDRF). This internationally accepted approach has been adopted to ensure that there is a clear understanding of the term “manufacturer” across international markets. For further details see: http://www.imdrf.org/
6.4. Eligibility principles and eligibility criteria

To meet the needs of WHO Member States and UN agencies, the prequalification scope is defined according to the following prequalification eligibility principles:

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

The eligibility criteria are periodically reviewed by WHO, in consultation with other UN agencies and relevant experts, and made publicly available by WHO on its website. WHO also obtains input from WHO Member States to determine which male circumcision devices are of priority to them.

7. Applying for WHO prequalification

To ensure that WHO can prequalify MCDs as efficiently as possible, manufacturers should be fully prepared for the prequalification assessment process when they apply for WHO prequalification. Manufacturers may wish to contact the WHO Prequalification Team – Male Circumcision Devices Assessment (email: diagnostics@who.int) and/or the WHO Prequalification Team – Inspections services (email: prequalinspection@who.int) to commence discussions on the prequalification assessment processes and requirements before applying. In addition, the WHO Prequalification webpage provides guidance materials to assist manufacturers in ensuring their readiness for WHO prequalification.³

The manufacturer must complete an application form (WHO document PQMC_015 Application form) and must provide WHO with all requested supporting documentation in accordance with the WHO document PQMC_017 Instructions for the completion of the application form.

The application form and the requisite attachments (authorization letter and instructions for use) must be submitted, preferably electronically, by the manufacturer to WHO for review. A completed application form provides summary information about the product, its regulatory version and the manufacturer. The details provided in this form will inform WHO in its decision on whether or not the product submitted is eligible for prequalification assessment. It is also used to determine the regulatory version intended for prequalification and to plan for each of the components of the prequalification assessment process. It is therefore important for the manufacturer to ensure that the information supplied in the application form is accurate and complete.

The prequalification application form and supporting documentation will be reviewed by WHO against the established eligibility criteria to determine the product’s eligibility for prequalification assessment. If necessary, the manufacturer may receive a communication from WHO requesting additional information and/or clarifications to assist it in the eligibility decision. The manufacturer must provide WHO with the information and/or clarifications so requested within the deadlines prescribed by WHO. WHO will inform the manufacturer in writing of WHO’s decision concerning whether or not the product is eligible for prequalification assessment.

If a product is found to be eligible for prequalification assessment, WHO will request the manufacturer to complete, sign and return to WHO the Letter of Agreement, which will serve: (i) as an agreement between WHO and the manufacturer on the participation of the product in the

³ https://www.who.int/diagnostics_laboratory/evaluations/prequalification_male_circumcision_devices/en/PQMC_007 v2 15 April 2019 (This document version supersedes any previous document versions)
prequalification assessment process, and (ii) as the manufacturer’s acceptance of, and commitment to comply with, the provisions of the prequalification assessment process. A prequalification dossier screening and assessment fee will also be payable by the manufacturer.

Before the prequalification assessment of a product that has been found eligible by WHO may commence, the manufacturer must deliver to WHO: (i) a signed and completed Letter of Agreement, and (ii) proof of payment the applicable prequalification fee.

8. Prequalification assessment

8.1. Prequalification assessment process

The WHO prequalification assessment process for MCDs consists of the following components (see Figure 1):

- review of a product dossier, including review of clinical evidence;
- inspection of manufacturing site(s); and
- labelling review.

Figure 1 Prequalification of MCDs: assessment process
8.2. Product dossier submission and screening

For a prequalification assessment, WHO will formally invite the manufacturer to submit a product dossier together with the duly signed Letter of Agreement and proof of payment of the dossier screening fee. Before the prequalification assessment may commence, the manufacturer must: (i) compile and submit to WHO the product dossier, as prescribed by WHO documents PQMC_018 *Instructions for compilation of a product dossier* and PQMC_049 *Product dossier checklist*; (ii) complete, sign and return to WHO the Letter of Agreement; and (iii) provide WHO with proof of payment of the applicable prequalification dossier screening fee. Manufacturers should not submit a product dossier or pay the prequalification fee, unless instructed to do so by WHO. Product dossiers that are submitted without a request from WHO will be destroyed without review.

Information that was previously submitted in the pre-submission form will also be considered by WHO during the review of the product dossier.

Manufacturers must ensure that the content of the product dossier is consistent with the information submitted in the pre-submission form and that any changes in the information submitted in or as part of the pre-submission form are promptly notified in writing to WHO.
The product dossier should only include information in support of the product name, product code(s), regulatory version and manufacturing site(s) indicated as eligible by WHO.

Once the product dossier has been received by WHO, it will be screened for completeness by WHO staff before being reviewed. This screening is aimed at ensuring that all requisite sections of the product dossier have been submitted and as such does not take into consideration the technical appropriateness of all the information provided in the product dossier. If the product dossier is incomplete, the manufacturer will be informed in writing that an incomplete dossier has been received and will be requested to provide supplemental information to complete the dossier within a specified deadline. The manufacturer will be given two opportunities to submit the required supplemental information within the deadlines set by WHO. In the event of non-compliance, the product dossier will be rejected on grounds of incompleteness and the application will be cancelled pursuant to section 10.3 (Cancellation of the application). Dossiers that are considered complete following the screening will be retained by WHO for dossier review. WHO will inform the manufacturer in writing on the outcome of the dossier screening.

8.3. Prequalification assessment components

8.3.1. Product dossier review, including clinical evidence review

WHO reviews the product dossier with the purpose of:

- assessing evidence in support of safety and performance of the product; and
- assessing the product design and manufacture.

The information submitted in the product dossier will be assessed by WHO staff and/or external experts (assessors) appointed by WHO after submission of proof of payment of the applicable prequalification assessment fee. Assessors 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. Assessors involved in the product dossier review must have appropriate qualifications and expertise in the relevant fields and must comply with the confidentiality and conflict of interest rules of WHO. The assessors will act as temporary advisers to WHO.

The product dossier should contain clinical evidence that demonstrates conformity of the device with the Essential Principles 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 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.

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4 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.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-n47.pdf

5 ISO 14155-1:2003
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 assessment of product dossiers will be conducted in accordance with standard operating procedures (SOPs) established by WHO for that purpose so as to ensure uniformity in evaluation and timeliness of assessment activities. If needed, WHO may provide training to the assessors.

Any deficiencies in the documentation submitted and/or in the data that are identified in the product dossier review will be communicated in writing to the manufacturer by WHO. A corrective action plan that details the amendments needed to correct the deficiencies (i.e. responses to comments; documentation and/or data that is missing) and deadlines for their submission must be provided by the manufacturer to WHO. The manufacturer will have the opportunity to submit up to two corrective action plans and, provided that the corrective action plan is accepted by WHO, only one amendment to the original product dossier will be permitted. The prequalification assessment procedure is usually suspended (i.e. WHO will not undertake any further action) until a corrective action plan has been submitted by the manufacturer and accepted by WHO. In certain cases, WHO may agree, in its sole discretion, to permit the manufacturer to correct specific nonconformities after prequalification provided that the manufacturer commits in writing to correct them by an agreed upon deadline. Such a “commitment to prequalification” will be reflected in the WHO prequalification public report and will be verified during the re-inspection. Failure to comply with prequalification comittments within agreed deadlines will result in the delisting from the WHO list of prequalified MCDs.

The manufacturer may request a hearing or meeting with WHO to clarify issues identified during dossier review. WHO may provide technical guidance and specifications to manufacturers to facilitate compliance with WHO requirements.

If the product successfully meets the WHO prequalification requirements, a summary of the product dossier review will be included in the WHO prequalification public report. If the product dossier does not meet WHO prequalification requirements or if any of the other conditions outlined under section 10.3 (Cancellation of the application) is met, the prequalification application will be cancelled.

### 8.3.2. Inspection of manufacturing site(s)

The inspection of the manufacturing site(s) is conducted to assess compliance of the manufacturer’s quality management system and manufacturing practices with international standards, such as the quality management standard ISO 13485:2003 and ISO 13485:2016 Medical devices — Quality management systems — Requirements for regulatory purposes and other relevant international standards and guidelines produced by GHTF and IMDRF. However, the WHO inspection of the manufacturing site will focus on the suitability of the implemented processes and procedures for the reliable supply of MCDs to WHO Member States. Therefore, customer-related issues that may be covered only in general terms in ISO 13485 are inspected in detail. Importantly, the inspection will also verify the content of the product dossier through review of reports and raw data onsite, and interviews with the personnel involved.

If serious or critical nonconformities of public health concern are identified in connection with an inspection, WHO reserves the right to use, publish, issue, share with with relevant authorities of WHO Member States as well as with UN agencies and other relevant intergovernmental organizations, and/or make publicly available (in each case, pursuant to the provisions of this document, including provisions regarding the protection of any commercially sensitive confidential information of the manufacturer) any outcomes, reports and/or results—whether in draft or final
form, and whether positive or negative—arising from or relating to the prequalification assessment process, including without limitation any WHO Notices of Concern, WHO Notices of Suspension, WHO information notices for users and/or manufacturer-issued field safety notices.

The manufacturer should carefully read the information set out in the WHO document PQDx_014. Version MC_0 – Information for manufacturers on the inspection of manufacturing site(s) for more information on the requirements of inspection, reports, nonconformities and Notices of Concern.

Under the prequalification assessment, the initial inspection of the manufacturing site will be performed in two stages. The stage 1 inspection, usually a desk audit, will evaluate the documentation related to the quality management system to ensure readiness for the stage 2 inspection. General information about the documented quality management system (including the quality manual and manufacturing processes, organigram, workflows, critical suppliers and floor plan) will be reviewed during the stage 1 inspection to establish the readiness of the manufacturer’s quality management system and to prepare for an on-site visit. Any issues of concern will be communicated to the manufacturer. A satisfactory stage 1 inspection is a precondition for proceeding to the stage 2 inspection.

The stage 2 inspection will comprehensively evaluate the effective implementation of the quality management system and production processes through an onsite(s) inspection. The inspection team is composed of WHO staff, external experts (inspectors) appointed by WHO as well as, potentially, interpreters and observers. The inspectors involved in the onsite(s) inspection should have appropriate qualifications and expertise in the relevant fields, must comply with the confidentiality and conflict of interest rules of WHO, and will act as temporary advisers to WHO. Representatives of the national regulatory authorities (NRAs) and other WHO employees may accompany the inspection team to the manufacturing site(s) as observers or for training purposes.

8.3.2.1. Report on the inspection of the manufacturing site(s)

A preliminary non-conformance report detailing issues of concern (if any) will be provided to the manufacturer on the final day of the inspection. A final inspection report, including the graded nonconformities will be issued to the manufacturer after the inspection of the manufacturing site(s).

All nonconformities must be corrected by the manufacturer through suitable corrective actions addressing the root cause of each nonconformity. The manufacturer will have the opportunity to submit up to two corrective action plans. Depending on the nature and number of nonconformities objective evidence of the effective implementation of proposed corrective actions may be required. WHO will assess the information provided and decide whether the corrective action plan can be accepted. Conformity with prequalification requirements will be established based on assessment of such information. In some instances, the number and criticality of nonconformities may require that the effective implementation of proposed corrective actions needs to be verified in a follow up inspection, before the nonconformities can be closed off.

A summary of the findings of the inspection of the manufacturing site(s) will be included in the WHO prequalification public report, if the product successfully meets the WHO prequalification requirements. In certain cases, WHO may agree, in its sole discretion, to permit the manufacturer to correct specific nonconformities after prequalification, provided that the manufacturer commits in writing to address them by an agreed upon deadline. Such a “commitment to prequalification” will be reflected in the WHO prequalification public report and will be verified during the re-inspection. Failure to comply with prequalification commitments within agreed deadlines will result in the delisting from the WHO list of prequalified MCDs. If the manufacturer does not meet WHO

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6 The stage 1 inspection may also be performed on-site.
prequalification requirements or if any of the other conditions outlined in section 10.3 (Cancellation of the application) are met, the prequalification application will be cancelled.

8.3.3. Labelling review

Product labelling is considered a critical element of the evidence submitted for prequalification assessment. Only clear and comprehensive labelling will effectively communicate the product information to the intended user and ensure the safe use of the prequalified MCD.

The version of the instructions for use (IFU) of the product which is submitted with the application form will be considered during the prequalification assessment. The manufacturer must obtain WHO’s written agreement prior to implementing any changes to this version of the instructions for use; otherwise, the application may be cancelled.

The product labelling will be reviewed as part of the application form, product dossier and inspection of manufacturing site(s). The IFU is reviewed for clarity, correctness, consistency with the information submitted in the product dossier and in the technical documentation, and with international guidance and requirements, and suitability for the target user group in WHO Member States. The overall feedback on the labelling review will be provided to the manufacturer after all assessment components have been completed. If requested by WHO, the manufacturer must amend the labelling before the product can be prequalified.

The agreed product labelling will be included in the prequalification public report.

9. Deadlines for prequalification assessment and requests for extensions

WHO will perform assessment activities within agreed target timelines.

The manufacturer will be assigned a deadline for the submission of requested information each time such a request is issued by WHO, and the manufacturer will use its best efforts to provide WHO with all requested information by such deadline. In addition, WHO will request that the inspections of manufacturing site(s) are scheduled within a defined time frame to be communicated by WHO.

The manufacturer is allowed to request an extension of the timeline for submission of the requested information or for scheduling a manufacturing site inspection.

10. Outcome of the prequalification assessment

10.1. Reporting and communication of the results of the prequalification assessment

As part of the prequalification assessment process, WHO may share the manufacturer’s application and related information with interested NRAs, subject to WHO entering into an appropriate confidentiality undertaking with each such NRA. Furthermore, the outcome of any joint review of information by WHO and NRA(s) may be utilized by WHO, at its discretion, as part of the prequalification assessment process.

Each dossier review report, clinical evidence review report, manufacturing site(s) inspection report and labelling review report will be finalized according to the relevant SOPs and format established by WHO, describing the findings and including requests and recommendations to the manufacturer. The assessment reports will be communicated in writing to the manufacturer. If any additional information is required, or if corrective action has to be taken by the manufacturer, WHO will postpone its decision on the acceptability of the product and/or manufacturing site(s) concerned until, as applicable: (i) such information has been provided by the manufacturer, assessed and found satisfactory by WHO, and/or (ii) such corrective action has been taken by the manufacturer and found satisfactory by WHO, in light of the specified standards.
As WHO is responsible for the prequalification assessment process, the ownership of the reports arising from or relating to the prequalification assessment process 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, 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 to the protection of commercially sensitive confidential information, WHO will publish on the WHO website and make publicly available the following information in connection with the prequalification assessment process:

- the names of products and of manufacturers that have applied for prequalification, the product code(s) submitted for prequalification and the prequalification status of each application;
- a WHO prequalification public report summarizing the findings of the prequalification assessment (including the findings from the dossier review, clinical evidence review and manufacturing site(s) inspection); and
- any negative outcomes of the prequalification assessment, including product alerts such as WHO information notices for users, WHO notices of suspension and/or WHO Notices of Concern.

Notwithstanding any of the foregoing, WHO reserves the right to use, publish, issue, share with relevant authorities of WHO Member States as well as with UN agencies and other relevant intergovernmental organizations, and/or make publicly available (in each case, in accordance with the provisions of this document, including provisions regarding the protection of any commercially sensitive information of the manufacturer) any outcomes, reports, notices and/or results—whether in draft or final form, and whether positive or negative—of the prequalification assessment process including, but not limited to, the dossier review, clinical evidence review and/or manufacturing site inspection, and including any confidential information to which WHO may gain access in the course of the prequalification process.

**10.2. Successful prequalification**

Once WHO is satisfied that the prequalification assessment process is complete for the relevant product, and that the product meets the WHO prequalification requirements, the product bearing a specific product name, product code(s) and regulatory version, as manufactured at the specific manufacturing site(s) inspected, will be included in the WHO list of prequalified MCDs. The WHO list of prequalified MCDs will be compiled in accordance with an SOP established by WHO for final decision-making on inclusion in that list. The list will be published on the WHO website and will specify the prequalified product name, the respective product code(s), regulatory version, the manufacturer’s name, the manufacturing site(s), the product packaging and the year in which the product was prequalified.

The manufacturer will receive a letter of prequalification from WHO informing it of the outcome of the overall prequalification assessment of the product. Once the product is included in the WHO list of prequalified MCDs, the manufacturer will be responsible for:

- fulfilling prequalification commitments;
- annual reporting;
• reporting of changes;
• post-market surveillance obligations;
• receiving re-inspections; and
• continued compliance with WHO prequalification technical specifications, as applicable.

The decision to include the product in the WHO list of prequalified MCDs is made based upon information available to WHO at the time of the prequalification assessment, including information obtained as a result of the product dossier review, the review of the clinical evidence, the inspection of manufacturing site(s) and/or the labelling review conducted by WHO. This decision is subject to change on the basis of new information that may become available to WHO.

**NOTE:** If serious or critical non-conformities or concerns (including with respect to quality, safety and/or performance) are identified in connection with the prequalification assessment of a product and/or a prequalified product, WHO reserves the right to use, publish, issue, share with with relevant authorities of WHO Member States as well as with UN agencies and other relevant intergovernmental organizations, and/or make publicly available (in each case, pursuant to the provisions of this document, including provisions regarding the protection of any commercially sensitive information of the manufacturer) any outcomes, reports, notices and/or results—whether in draft or final form, and whether positive or negative—arising from or relating to the prequalification assessment process and/or prequalified product, including without limitation any WHO Notices of Concern, WHO Notices of Suspension, WHO information notice to end users and/or manufacturer-issued field safety notices. Consequently, WHO may delist the product after evaluation of the evidence and risk–benefit assessment, or may suspend the product until results of further investigations become available and are assessed by WHO. WHO may re-list the product only after the aforementioned evidence, risk–benefit and other assessments, and investigation results are considered acceptable by WHO.

Manufacturers must understand that it is not WHO’s mandate to issue any approvals, certificates or licences for MCDs. This responsibility lies with the NRA of each country. Furthermore, WHO does not, as a matter of policy, endorse any specific commercial product over others. As mentioned above, the purpose of the WHO prequalification of MCDs is to provide guidance to interested UN agencies and WHO Member States in their procurement decisions. In this regard, the results of the prequalification assessment, the participation in the WHO prequalification assessment process, the inclusion of any product in the WHO list of prequalified MCDs and/or the WHO name and emblem, may not be used by 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 that is included in the WHO list of prequalified MCDs.

**10.2.1 Correcting nonconformities identified during assessment and prequalification commitments**

Nonconformities identified as part of any component of the prequalification assessment must be corrected by the manufacturer within the deadlines agreed with WHO. All critical nonconformities must be corrected before the product is prequalified. In certain cases, WHO may agree, in its sole discretion, to permit the manufacturer to correct specific nonconformities after prequalification occurs, provided that the manufacturer commits in writing to correct them by an agreed upon deadline. Such commitments to prequalification must be fulfilled by the manufacturer within the agreed deadlines in order to keep the prequalification status of the product. Failure to fulfill all
prequalification commitments within the agreed deadlines will lead to delisting of the product from the WHO list of prequalified MCDs.

10.3. Cancellation of the application

WHO reserves the right to cancel the application for a specific product at any time or stage of the prequalification assessment procedure if:

- the product dossier does not contain all of the required information, including the clinical evidence, or does not meet WHO prequalification requirements; and/or
- the manufacturer is not able to, or fails to, provide the required or requested information within a specified deadline; and/or
- the manufacturer is not able to, or fails to, implement any corrective actions which WHO may require within a specified deadline; and/or
- the information supplied is inadequate to complete the prequalification assessment in a timely manner.

In this case, the manufacturer will not be allowed to re-apply for WHO prequalification assessment for a period of time determined by WHO, usually one year from the date of notification of cancellation, unless otherwise agreed by WHO.

10.4. Withdrawal from the prequalification assessment

WHO provides the manufacturer with the right to withdraw its application for prequalification assessment at any time or stage. To exercise this right of withdrawal, the manufacturer must provide WHO with written notice specifying the product(s) to be withdrawn. In this case, the manufacturer will not be allowed to re-apply for WHO prequalification assessment for the products so withdrawn for a period of time determined by WHO, usually one year from date of notification of withdrawal, unless otherwise agreed by WHO.

10.5. Reporting and communication of outcomes after withdrawal or cancellation of an application

The cancellation or withdrawal, at any time and for any reason, of an application for prequalification assessment of a specific product will not prejudice or otherwise affect WHO’s rights to use, publish, issue, share with relevant authorities of WHO Member States as well as with UN agencies and other relevant intergovernmental organizations, and/or make publicly available (in each case, in accordance the provisions of this document, including provisions regarding the protection of any commercially sensitive information of the manufacturer) any outcomes, reports, notices and/or results—whether in draft or final form, and whether positive or negative—arising from or relating to the prequalification assessment process, including without limitation any WHO Notices of Concern, WHO Notices of Suspension, WHO information notices for users and/or manufacturer-issued field safety notices.

10.6. Reporting and communication of outcomes after delisting or suspension of a product

If the prequalification assessment and/or a prequalified product is suspended or delisted, at any time and for any reason, such suspension or delisting will not prejudice or otherwise affect WHO’s rights to use, publish, issue, share with with relevant authorities of WHO Member States as well as with UN agencies and other relevant intergovernmental organizations, and/or make publicly available (in each case, in accordance the provisions of this document, including provisions regarding the protection of any commercially sensitive information of the manufacturer) any outcomes, reports, notices and/or results—whether in draft or final form, and whether positive or negative—arising from or relating to the prequalification assessment process, including without
limitation any WHO Notices of Concern, WHO Notices of Suspension, WHO information notices for users and/or manufacturer-issued field safety notices.

### 11. Prequalification fees

The cost of the activities required to assess MCDs for prequalification will be covered in part by the manufacturer. The non-refundable prequalification fee will contribute to the costs associated with review of the application form for determining eligibility for prequalification, product dossier screening, product dossier review, inspection of manufacturing site(s), labelling review and dissemination of prequalification information.

Manufacturers should note that WHO reserves the right to decide, based on the prequalification assessment findings, whether a product meets the requirements to become prequalified. Therefore, payment of the prequalification fees does not guarantee that the product will be prequalified and/or that, if prequalified, the product will retain its prequalification status for any minimum duration.

If the assessment of a change to a prequalified MCD or to the quality management system is required, the manufacturer may need to pay an additional fee.

### 12. Duration of the validity of the prequalification status

WHO will reassess products included in the WHO list of prequalified MCDs and their associated manufacturing sites at intervals determined by WHO using a risk-based approach. If, as a result of this reassessment, it is found that a product and/or specified manufacturing site(s) no longer meets WHO requirements, such products will be removed from the list. Failure of a manufacturer to participate in the reassessment procedure will also lead to delisting of the product from the WHO list of prequalified MCDs.

#### 12.1. Fulfilment of prequalification commitments

Commitments to prequalification must be fulfilled by the manufacturer within the agreed deadlines in order to keep the prequalification status of the product. Failure to meet prequalification commitments within the agreed deadlines will lead to delisting of the product(s) from the list of prequalified MCDs.

#### 12.2. Annual reporting

For all prequalified products, the manufacturer must submit to WHO an annual report that details sales data and all categories of complaints in a summarized form. The annual report, in the format prescribed by WHO, must be submitted by the manufacturer to WHO every year following prequalification. The manufacturer will receive a letter from WHO requesting submission of the annual report together with the prescribed report format. The report for the previous calendar year must be submitted no later than 28 February. The information provided in the annual report will inform WHO’s decision on the frequency of re-inspections.

#### 12.3. Submission of changes for prequalified MCDs

WHO prequalifies an MCD as it is submitted to and assessed by WHO at a particular point in time. To meet the WHO prequalification requirements, the manufacturer must establish, maintain and

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7 PQMC_299 Prequalification fees for male circumcision devices
8 PQMC_121 Reportable changes to a WHO prequalified male circumcision device
implement a procedure for categorizing and documenting any changes to the product and/or the quality management system. This procedure must be available as part of the product dossier and during the inspection of the manufacturing site(s).

The manufacturer of product(s) included in the WHO list of prequalified MCDs must comply with the duties and responsibilities set out in WHO document PQMC_121 – Reportable changes to a WHO prequalified male circumcision device including, without limitation, the obligation to report to WHO:

- changes to the prequalified product or its design, labelling or manufacture;
- changes to the quality management system under which the product was designed and manufactured; and/or
- other reportable administrative changes.

To determine whether a change to the product, including its design, labelling and manufacture, or to the quality management system, requires reporting to WHO, the manufacturer should evaluate the potential effect this change may have on the safety, quality or performance of the product.

For all reportable changes to a prequalified product, the manufacturer must submit to the WHO Prequalification of MCDs team the WHO document PQDx_119 – Change report form for a WHO prequalified in vitro diagnostic and supporting documentation and, in some cases, a new prequalification application.

The manufacturer must communicate to WHO its intent to introduce a reportable change well in advance (i.e. early in the process of designing and validating the change), in order to allow sufficient time for WHO to assess the change before its implementation. WHO will not approve any changes without due assessment. Depending on the type of change, the assessment may also include an inspection of the manufacturing site(s) and/or the review of clinical evidence.

Once the change report form and supporting documentation are received by WHO, they will be screened for completeness and, provided all the required information has been supplied, they will undergo assessment by WHO. If any aspect of the change report form or the supporting documentation is incomplete, the manufacturer will be informed in writing and requested to complete it within a specified deadline set by WHO. If the manufacturer fails to complete the aspect within the specified deadline, the product may be removed from the list of prequalified MCDs.

WHO will inform the manufacturer in writing of the outcome of its assessment of the change. The manufacturer will also be notified if WHO deems (based on the nature of the change and its potential impact on the quality, safety and/or performance of the product), that an inspection of the manufacturing site(s) and/or the review of clinical evidence is also required.

Once WHO is satisfied that the prequalification change assessment of a product is complete and provided that the overall findings demonstrate, as determined by WHO, that the product continues to meet all WHO prequalification requirements, then the WHO list of prequalified MCDs will be updated, as necessary, to reflect the relevant change accepted by WHO.

If the submitted documentation supporting the change does not meet WHO prequalification requirements or if all the requested information is not provided by the manufacturer within the specified deadline, WHO will reject the change. The impact of such a decision on the prequalification status of the prequalified MCD will be communicated to the manufacturer in writing by WHO.

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9 In some cases, changes affect the safety and performance of the product to such a magnitude that a new application for WHO prequalification assessment is required. This will occur where it is deemed that the changes have resulted in a product or application information of substantial difference to that which was prequalified. In these cases, WHO will notify the manufacturer that a new application to WHO prequalification is required.
12.4. Post-market surveillance of WHO prequalified MCDs

Post-market surveillance monitors the continued compliance of WHO prequalified products with WHO prequalification requirements. The WHO post-market surveillance system includes proactive collection of information on quality, safety and performance of the MCD after it has been prequalified, as well as reactive reporting for the notification and evaluation of complaints, enabling appropriate action to be taken.\(^\text{10}\)

As soon as an MCD is accepted into the prequalification assessment process, and as long as that MCD is included in WHO’s list of prequalified MCDs, the manufacturer must, as a condition of prequalification, follow the guidance contained in the WHO document entitled *Post-market surveillance of in vitro diagnostics* and, in particular, comply with the manufacturer’s obligations set forth in that document including, for example, the obligation to undertake the following post-market surveillance activities:

- To notify WHO of any events relating to the MCD that have affected (or could have affected) the performance of the MCD, safety of the person being tested, safety of users of the MCD or safety of any person associated with the MCD, including:
  - any serious adverse effect, which should be reported to WHO within 10 days;
  - any moderate adverse event or any change in the trend of mild adverse events, which should be reported to WHO within 30 days; and
  - all complaints (as well as all serious, moderate and mild adverse events), which must be reported to WHO annually in the periodic summary report.

In the case of a complaint, WHO will request the manufacturer to provide (and, upon such a request, the manufacturer must promptly provide to WHO) further information relating to the complaint, including details regarding the investigation undertaken, and any corrections and corrective actions taken:

- to activate the manufacturer’s complaint-handling system, to inform WHO of reportable adverse events, and to encourage end users to report on problems experienced with the use of the MCD;
- to notify WHO of all events that require field-safety corrective actions, such as withdrawal of products from sale or distribution, physical return of the MCD to the manufacturer or destruction of the product (e.g. recall), product exchange, product modification(s) or provision of additional advice 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 to laboratories designated by WHO, free-of-charge and delivered duty paid, for post-market surveillance lot verification testing.

WHO will investigate any complaint concerning a prequalified MCD that is communicated to WHO by end users or by manufacturers. First, WHO will notify the manufacturer and, depending on the nature of the complaint, may also notify NRAs, relevant authorities of any interested WHO Member State and/or interested UN agencies of the complaint.

WHO reserves the right to use, publish, issue, share with with relevant authorities of WHO Member States as well as with UN agencies and other relevant intergovernmental organizations, and/or make publicly available (in each case, pursuant to the provisions of this document, including provisions regarding the protection of any commercially sensitive information of the manufacturer)

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\(^{10}\) The WHO post-market surveillance system does not replace any national post-market surveillance requirements.
any outcomes, reports and/or results—whether in draft or final form, and whether positive or negative—of:

- any investigation relating to a complaint concerning any product and/or prequalified product;
- any field safety corrective action;
- any WHO Notices of Concern, WHO Notices of Suspension or WHO information notices for users;
- any manufacturer-issued field safety notices; and
- any confidential information to which WHO may gain access in the course of any of the foregoing.

WHO will review the investigation conducted by the manufacturer to ensure that it complies with scientific principles and is in accordance with international guidance and standards. WHO reserves the right to request a special inspection to verify that correction and corrective actions have been implemented.

12.5. Routine re-inspection

Routine re-inspections will be conducted to ensure continued compliance with prequalification requirements. Routine re-inspections will typically take place every three and up to five years after prequalification of a product, unless an earlier re-inspection is deemed necessary by WHO.

12.6. Compliance with technical specification applicable to WHO Prequalification of Male Circumcision Devices

The purpose of the WHO Prequalification Technical Specifications Series is to provide technical guidance to manufacturers of MCDs seeking WHO prequalification. Manufacturers must comply with the requirements laid down in the relevant publication in the WHO Prequalification Technical Specifications Series.

For products prequalified before the issuance of the relevant publication in the WHO Prequalification Technical Specifications Series, a transition period will apply. Manufacturers must comply with the relevant technical specifications as outlined in the aforementioned Series within three years from their publication. Compliance with the Technical Specifications will be verified during the re-inspection. Failure to comply with the relevant Technical Specifications will result in the delisting of the product from the WHO list of prequalified MCDs.

13. Confidentiality

WHO assessors, inspectors and the designated evaluating sites will treat all information to which they will gain access during the assessments, inspections and evaluations, or otherwise in connection with the discharge of their responsibilities in regard to this prequalification procedure, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

WHO assessors, inspectors and the designated evaluating sites will take all reasonable measures to ensure that confidential information:

- is not used for any purpose other than the assessment, inspection and evaluation 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.
WHO assessors, inspectors and evaluating sites 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 by the manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by 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; or
- was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such confidential information; or
- is required to be disclosed by law, provided that WHO shall in such case immediately notify the manufacturer in writing of such obligation and shall provide adequate opportunity to the manufacturer to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).

14. Conflict of interest

Before undertaking the work, each external inspector, assessor and the representative of the evaluating site will also (in addition to the above-mentioned confidentiality undertaking) be required to complete and sign the WHO declaration of interests form.

If, based on the above-mentioned declaration of interests, 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 assessor or inspector in question to undertake the work, then he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interests is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All inspectors furthermore agree that, at the manufacturer’s request, WHO will advise the manufacturer, in advance, of the identity of each inspector and the composition of the team performing the manufacturing 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 WHO before the inspection visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer may object to a team member’s participation in the manufacturing site visit. Such an objection must be made known in writing by the manufacturer to WHO within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

15. Disputes – privileges and immunities of WHO

In the event of any dispute or disagreement between the manufacturer and WHO arising from or relating to the prequalification assessment process, an SOP established by WHO for the handling of such disputes and disagreements will be followed to discuss and resolve the issue.

By virtue of WHO’s status as a specialized agency of the UN, WHO, its officials and experts performing missions for WHO (including, e.g. the prequalification assessors and inspectors) enjoy privileges and immunities under national and international laws and conventions, including the
Convention on the Privileges and Immunities of the Specialized Agencies, adopted by the General Assembly of the United Nations on 21 November 1947 (the 1947 Convention). Nothing contained in or relating to this document or the prequalification assessment will constitute or be deemed as a waiver of any of the privileges or immunities which WHO, its officials and/or experts performing missions for WHO enjoy pursuant to the 1947 Convention or otherwise under any national or international law, convention or agreement, and/or as submitting WHO, its officials and/or experts aforesaid to any national court jurisdiction.

16. Relevant documents

The following documents provide information to guide the manufacturer through the requirements of the WHO prequalification assessment for Male Circumcision Devices.11

- Instructions for the completion the application form. Geneva: World Health Organization; (PQMC_017).
- Information for manufacturers on the manufacturing site(s) inspection (assessment of the quality management system) Geneva: World Health Organization; (PQMC_014).

17. Contact information

Any enquiries regarding the WHO Prequalification of MCDs Programme should be addressed to: diagnostics@who.int

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