INSTRUCTIONS FOR COMPILATION OF A PRODUCT DOSSIER

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 assist manufacturers[1] in correctly compiling a product dossier for the purposes of WHO prequalification assessment.

Manufacturers who wish to submit a product dossier for a male circumcision device should read this document carefully and compile the product dossier in accordance with the requirements prescribed below.

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[1] For the purposes of prequalification of male circumcision devices, the following definition applies: **Manufacturer** means any natural or legal person[1] with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use, under his 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).

3. The Product Dossier

3.1. About the product dossier

There are many terms used internationally to describe a product dossier. These terms include: *standard technical documentation*, *technical file, summary technical documentation, product summary file, product master file,* and others. For the purposes of prequalification of male circumcision devices, WHO will use the term the *product dossier*, or simply the *dossier*.

The manufacturer is expected to prepare, and either hold or provide timely access to, technical documentation that shows how each male circumcision device was developed, designed and manufactured. This technical documentation, typically controlled in the manufacturer's quality management system (QMS), is often extensive and sections of it may be held in different locations. The documentation is revised to reflect any changes made during the life cycle of the male circumcision device through normal application of the manufacturer's QMS.

The product dossier is a selection of records and documents from this entire collection of records and documents that a manufacturer holds for a particular product. Manufacturers compile a product dossier from their existing technical documentation to provide evidence that the male circumcision device conforms to the *Essential Principles of Safety and Performance of Medical Devices* [2]. The information provided may include, for example, abstracts, high level summaries, or existing controlled documents, as appropriate, sufficient to communicate key relevant information and allow a reviewer to understand the subject to assess the validity of that information. Furthermore, the dossier should contain an *Essential Principles checklist (EP checklist)*. The content of the submitted product dossier should be traceable by the manufacturer for future reference.

NOTE: A "product" for prequalification of male circumcision devices means a specific product name, the respective product code(s), manufacturing site and regulatory version. All information submitted within the product dossier must refer to the specific "product".

The EP checklist should be created as part of the manufacturer's technical documentation and should be controlled by the manufacturer's QMS. It provides a tabular overview of the Essential Principles and identifies those that are applicable to the male circumcision device, the chosen method of demonstrating that the device conforms to each relevant Essential Principle and the reference of the controlled document that is relevant to a specific Essential Principle. While many controlled documents are referenced in the EP checklist, only some may be contained within the product dossier. The cited references to the controlled documents also allow easy identification of additional relevant documents and data.

This document describes the elements that a product dossier is expected to contain for the purposes of the WHO prequalification of male circumcision devices process. These WHO product dossier requirements are in-line with those expected by a number of National Regulatory

[2] The Global Harmonization Task Force document **GHTF/SG1/N41R9:2005 Essential Principles of Safety and Performance of Medical Devices** can be used as guidance document providing requirements of safety and performance. This document can be accessed through the following website: http://www.ghtf.org/sg1/sg1-final.html

Authorities. However, as WHO is not a regulator, certain requirements of particular Member States may not be addressed in the product dossier prepared for the WHO prequalification of male circumcision devices process.

WHO reviews the product dossier with the purpose of:

- assessing the product and how it performs;
- assessing the product manufacture; and
- determining if the manufacturer's quality management system is of an adequate standard to warrant a WHO prequalification site inspection.

NOTE: Information that was previously submitted in the *Prequalification of Male Circumcision Devices - APPLICATION FORM: Document PQMCx_015* will be considered during the review of the product dossier. Therefore, manufacturers should ensure that the content of the product dossier is consistent with the information submitted in the application form and that any changes in the information submitted with the respective application form are promptly notified to WHO. Furthermore, inadequacies identified at the application form stage and communicated by WHO to the manufacturer are expected to be addressed as part of the dossier submission.

3.2. Submission of a product dossier

If an application to the WHO Prequalification of Male Circumcision Devices Programme has been accepted for prequalification assessment, the manufacturer is notified. Subsequently, a formal letter of agreement is sent by WHO to the manufacturer. This document should be duly signed and sent back to before the process can proceed further. Upon completion of these requirements, WHO formally requests the manufacturer to submit a product dossier.

Upon request, two hard copies and one electronic copy of the product dossier must be posted to:

WHO Prequalification of Male circumcision devices
Diagnostics and Laboratory Technology (DLT)
World Health Organization
20 Avenue Appia
CH-1211, Geneva 27
Switzerland

NOTE: Manufacturers should not submit a product dossier to WHO unless requested to do so. Dossiers that are submitted without a request from WHO will not be given priority, and the dossier may be returned to the manufacturer without review.

Manufacturers should ensure that the dossier contains all the information as is prescribed in this document. Furthermore, content of the product dossier should be consistent with the information submitted in the application form. 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 is informed that an incomplete product dossier has been received and is requested to complete it within a specified time period.
The prequalification procedure may be terminated if the dossier does not contain the prescribed information, or where the information supplied is inadequate to complete the prequalification

assessment effectively or where the requested information is not provided by the manufacturer within a specified time period.

NOTE: Manufacturers should document each section of the product dossier as prescribed in this document. Where particular information indicated by this document is not included, a justification should be provided by the manufacturer. Leaving a section blank or stating "not applicable" is not considered acceptable without an appropriate justification.

3.3. Submission of product dossier amendments

Any issues identified during screening for completeness and communicated to the manufacturer must be addressed within the specified timelines in order to proceed to a full dossier assessment.

NOTE: When submitting the requested dossier amendments, manufacturers should only include the requested additional information. The entire product dossier should not be resubmitted. Two hard copies and one electronic copy of the requested product dossier amendments must be posted to the address stated under Section 3.2.

4. Dossier Format

4.1. Dossier clarity

A review of WHO processes has identified that poor-quality dossiers take much longer time for assessment. Therefore, product dossiers should be clear and well-organized to ensure that the prequalification assessment procedure is efficient for all applicants.

Poorly prepared dossiers may be returned to the applicant without full review. It is important to keep the needs of the review staff in mind when preparing the product dossier for submission. This will ensure that the request can be reviewed as quickly as possible.

4.2. Layout and order

Submissions formatted according to the WHO requirements prescribed in this document are preferred. However, submissions previously prepared for various National Regulatory Authorities may be accepted if all the information required by WHO is supplied, and if the information is fully cross-referenced to the WHO prequalification of male circumcision devices requirements using the *Product Dossier Checklist* document PQMC_049.

When submitting the product dossier, the following requirements should be fulfilled by the manufacturer:

- WHO requires two hard-copies of the dossier and one electronic-copy (CD or DVD) of the entire dossier. Any further amendments of the dossier must be submitted in two hard-copies and one electronic-copy.
- The hard-copy dossiers should be provided in a ring-binder. If the dossier comprises multiple volumes, the volumes should be clearly marked *1 of 2*, *2 of 2* etc. This also applies to product dossier amendments.
- The hard-copy should be clearly divided into sections, as prescribed in the *Product Dossier Checklist*, and the pages of each section should be numbered.

- The hard-copy should include a table of contents.
- The dossier should be submitted using the Product Dossier Checklist (document PQMC_049) as the first page. All sections of the dossier should be cross-referenced to this first page.
- The electronic copy of the dossier should be identical to the hard-copies in regard to content.

NOTE: The prequalification assessment process may be terminated if the dossier does not include the information prescribed in this document.

4.3. Language and units of measure

For the purposes of prequalification of male circumcision devices the following requirements apply:

- The dossier will be reviewed as an English language document.
- All documents presented in the dossier should be submitted in English (unless other arrangements have been made with WHO prior to submission of the dossier).
- Any translations of documents should be carried out by a certified translator. Details of the translator should be provided. The original and the translated document should be provided.
- Metric units shall be used, except where there are other internationally accepted units of measurement.

NOTE: All information related to the male circumcision device undergoing prequalification, including labeling, is provided in English. The manufacturer should ensure that translations into other languages are accurate and of good quality. Translations should be made by qualified medical translators and should be double checked by the manufacturer or the translation office. A poor quality translation may severely compromise the safety and performance of the male circumcision device. Therefore, male circumcision devices not complying with this requirement cannot be marketed as prequalified male circumcision devices .

5. The Product

5.1. Regulatory versions of this product

Different regulatory requirements apply to different international markets for male circumcision devices. Manufacturers who supply a male circumcision device into multiple countries often alter some aspects of a single product to comply with such varying regulatory requirements (for example: the information within the instructions for use, the intended purpose statements, batch release procedures, or information on the labels).

If the product submitted for prequalification has multiple regulatory versions, the manufacturer should provide information regarding these different regulatory versions. This information should cover all aspects that are different between these product regulatory versions including (but not limited to) differences in design, manufacturing, quality control, labeling, release for supply, and post-market practices.

NOTE: The information included in the product dossier should clearly indicate the product name, product code(s) and the regulatory version of the product submitted for prequalification assessment.

5.2. Device description

The dossier should include the following device descriptive information:

a) a general description including its intended use/purpose;
b) the intended patient population and medical condition to be treated or prevented and other considerations such as patient selection criteria;
c) principles of operation;
d) an explanation of any novel features;
e) a description of the accessories, other medical devices and other products that are not medical devices, which are intended to be used in combination with it;
f) a description or complete list of the various configurations/variants of the device that will be made available;
g) a general description of the key functional elements, e.g. its parts/components, its formulation, its composition, its functionality. Where appropriate, this will include: labelled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts/components, including sufficient explanation to understand the drawings and diagrams.
h) a description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body.

The instructions for use may be used to provide some of this information on the condition that a cross-reference to the different requirements is supplied in conjunction with the instructions-for-use.

5.3. Product specification

The dossier should contain a list of the features, dimensions and performance attributes of the male circumcision device, its variants and accessories (if such are within the scope of the dossier), that would typically appear in the product specification made available to the end user, e.g. in brochures, catalogues and the like.

5.4. Reference to similar and previous generations of the device

Where relevant to demonstrating conformity to the Essential Principles, and to the provision of general background information, the dossier should contain an overview of:

a) the manufacturer's previous generation(s) of the device, if such exist; and/or
b) similar devices available on the local and international markets.

5.5. Essential principles (EP) checklist

The product dossier should include an EP checklist that identifies:

- the Essential Principles of Safety and Performance;
- whether each Essential Principle applies to the male circumcision device and if not, why not;
- the method used to demonstrate conformity with each Essential Principle that applies;
- a reference for the method(s) employed (e.g., standard), and
- the precise identity of the controlled document(s) that offers evidence of conformity with each method used.

NOTE: The identity of the male circumcision device must be clearly identified on the EP checklist and should include the product name and product code(s). This information must be aligned with the information provided under Section 5.1. of the product dossier.

The method used to demonstrate conformity may include one or more of the following:

- conformity with recognized or other standards [3];
- conformity with a commonly accepted industry test method (reference method);
- conformity with appropriate in-house test methods that have been validated and verified;
- the evaluation of pre-clinical and clinical evidence, and
- comparison to a male circumcision device already available on the market.

The EP checklist should include a cross-reference to the location of such evidence both within the full technical documentation held by the manufacturer and within the dossier (when such documentation is specifically required for inclusion in the dossier as outlined in this instructions).A sample EP checklist is included in Annex A.

5.6. Risk analysis and control summary

A risk analysis should be undertaken to identify and address all known or foreseeable hazards for the product, taking into account such aspects as the user/s of the device, the patients on whom the device will be used and the technology involved. The dossier should contain a summary of the risks identified during the risk analysis process and a description of how these risks have been controlled to an acceptable level. Furthermore, the risk analysis should be part of the manufacturer's risk management plan.

Where specific standards or guidelines are recommended by WHO, these should be followed.

The information provided in the dossier should address possible hazards for the male circumcision device.

The results of the risk analysis should provide a conclusion with evidence that remaining risks are acceptable when compared to the benefits.

NOTE: The risk analysis and the instructions for use should be controlled by the manufacturer in full consistency with one another. All residual risks that could not be mitigated through design or protection measures should be addressed in the instructions for use as warnings and precautions and vice versa, all warnings and precautions mentioned in the instructions for use should originate from the risk analysis.

6. Design and Manufacturing Information

This section of the dossier should provide an overview of the design and manufacturing processes for the product under assessment, including a flow chart of the entire process. If design and manufacture is carried out at different sites, or by external suppliers, this should be indicated on the flow chart. The manufacturer should only refer to sites of suppliers of raw materials involved in critical design and manufacturing activities.

[3] Where the manufacturer demonstrates conformity with particular EP by claiming compliance with available standards, these standards should be identified.

Where Quality Management System certificates, or the equivalent, exist for any sites, certified copies should be annexed to the dossier.

6.1. Device design

6.1.1. Design overview

The dossier should contain information to allow a reviewer to obtain a general understanding of the design applied to the device. It should include a description of the critical parts/components provided or recommended for use with the product and their formulation, composition and functionality.
If design takes place at multiple sites, a controlling site should be identified.

6.1.2. Documentation of design changes

The dossier should include records of each design change and the reasons for these, together with any associated validation/verification data. The documentation should include evidence for believing that the change achieves the desired effect, and that the product continues to comply with the Essential Principles of Safety and Performance.

6.2. Manufacturing processes

6.2.1. Overview of manufacture

The dossier should contain information to allow the reviewer to obtain a general understanding of the manufacturing process. This section is not intended to take the place of more detailed information required for a QMS audit or other conformity assessment activity.

The manufacturer should provide details of each major step in the manufacturing process, to clarify the manufacturing steps. Include information on the manufacturing process for all components. The information may take the form of a process flow chart showing, for example, an overview of production including the technologies used, assembly, any in-process and final product testing, and packaging of the finished product.

Details of verification, validation and quality-control activities should be provided for all stages of design and manufacture (including purchased components, in-process products, and finished products).

6.2.2. Sites of manufacture

A list of all critical manufacturing sites that are involved in the manufacture of this product should be provided. This should cover all stages of manufacture (including design, warehousing, and quality-control stages of manufacture), but may not need to include the sites of supply of raw materials if they are not considered critical. For each site include:

- the name of site;
- the physical address of the site;
- a description of the component manufacture/stage of the manufacturing process carried out at the site;
- a description of the manufacturing site;
- a simple site plan highlighting production areas;
- the number of employees at the site;

- a description of any other manufacturing that occurs at this site.

NOTE: If a product is successfully prequalified, only product manufactured at the sites that have been presented in the product dossier will be considered to be prequalified. Any changes to sites of manufacture should be notified to WHO prior to implementation of the changes.

6.2.3. Key suppliers

List all key suppliers which supply ingredients/products/services for the manufacture of this product. For each supplier include:

- a description of the ingredient/product/service supplied;
- the name of the supplier;
- the physical address of the supplier's manufacturing facilities;
- details of the documented procedures used for the purchasing and verification of ingredients/products/services sourced from these suppliers.

If the manufacturer holds a certificate issued by a conformity assessment body and related to the quality management system, certified copies should be annexed to the dossier.

7. Product Verification and Validation

The product dossier should summarize the results of verification and validation studies undertaken to demonstrate conformity of the male circumcision device with the Essential Principles that apply to it. Such information would typically cover:

a) engineering tests;
b) laboratory tests;
c) simulated use testing;
d) any animal tests for demonstrating feasibility or proof of concept of the finished device;
e) any published literature regarding the device or substantially similar devices.

Such summary information may include:

a) declaration/certificate of conformity to a recognised standard(s) and summary of the data if no acceptance criteria are specified in the standard;
b) declaration/certificate of conformity to a published standard(s) that has not been recognised, supported by a rationale for its use, and summary of the data if no acceptance criteria are specified in the standard;
c) declaration/certificate of conformity to a professional guideline(s), industry method(s), or in-house test method(s), supported by a rationale for its use, a description of the method used, and summary of the data in sufficient detail to allow assessment of its adequacy;
d) a review of published literature regarding the device or substantially similar devices.

A summary of outcomes should be provided that contains enough information to allow WHO to assess the validity of that information. It should include any references to relevant international or published standards or guidelines that have been applied in the production of the data. It should also include a review of relevant published literature regarding the product or substantially similar products.

In addition, where applicable to the device, the dossier should contain detailed information on:

a) biocompatibility;
b) medicinal substances incorporated into the device, including compatibility of the device with the medicinal substance;
c) biological safety of devices incorporating animal or human cells, tissues or their derivatives
d) sterilisation;
e) animal studies that provide direct evidence of safety and performance of the device, especially when no clinical investigation of the device was conducted;
f) clinical evidence.

Detailed information on each performance claim should be provided and include:

- the complete study protocol
- the method of data analysis
- the complete study report
- the study conclusion.

Actual test result summaries with their acceptance criteria should be provided and not just pass/fail statements.

Where no new testing has been undertaken, the dossier should incorporate a rationale for that decision, e.g. biocompatibility testing on the identical materials was conducted when these were incorporated in a previous, legally marketed version of the device. The rationale may be incorporated into the EP checklist.

NOTE: In each submitted study, the product should be clearly identified (see section 5.1).

7.1. Biocompatibility

The dossier should contain a list of all materials in direct or indirect contact with the patient or user.

Where biocompatibility testing has been undertaken to characterize the physical, chemical, toxicological and biological response of a material, detailed information should be included on the tests conducted, standards applied, test protocols, the analysis of data and the summary of results. At a minimum, tests should be conducted on samples from the finished, sterilized (when supplied sterile) device.

7.2. Medicinal Substances

Where the device incorporates, or its use requires, a medicinal substance(s), the dossier should provide detailed information concerning that medicinal substance, its identity and source, the intended reason for its presence, and its safety and performance in the intended application.

7.3. Biological Safety

The dossier should contain a list of all materials of animal or human origin used in the device. For these materials, detailed information should be provided concerning the selection of

sources/donors; the harvesting, processing, preservation, testing and handling of tissues, cells and substances of such origin should also be provided.

Process validation results should be included to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents.

The system for record-keeping to allow traceability from sources to the finished device should be fully described.

7.4. Sterilization

Where the device is supplied sterile, the dossier should contain the detailed information of the initial sterilization validation including bio burden testing, pyrogen testing, testing for sterilant residues (if applicable) and packaging validation.

Typically, the detailed validation information should include the method used, sterility assurance level attained, standards applied, the sterilization protocol developed in accordance with those standards, and a summary of results.

Evidence of the ongoing revalidation of the process should also be provided. Typically this would consist of arrangements for, or evidence of, revalidation of the packaging and sterilization processes.

7.5. Animal Studies

Where studies in an animal model have been undertaken to provide evidence of conformity with the Essential Principles related to functional safety and performance, detailed information should be contained in the dossier.

The dossier should describe the study objectives, methodology, results, analysis and conclusions and document conformity with Good Laboratory Practices. The rationale (and limitations) of selecting the particular animal model should be discussed.

7.6. Clinical Evidence

The dossier should contain the 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.[4]

7.6.1. Clinical study - Manufacturer

All performance claims should be supported by well-designed studies which have been carried out or coordinated by the manufacturer. Provide information for these clinical studies which should include:

- A detailed written plan and protocol which explains the intent of the study and the way in which the study was performed.
- The date/s on which the study was performed and by which site.
- A written report on the outcome of study. This report should explain how the study results support the product clinical claims. Any anomalous results, or results that are not within predetermined specifications, should be clearly explained or justified.
- Clear identification of the product and product version that is being evaluated.
- Details of the product lots/batches used for the evaluation, including lot number, date of expiry, and the storage conditions of the product prior to and during the study.
- Details of the geographical region and the clinical status of the subjects included in the study.
- Full details of the methods used to define the clinical status of the subjects.
- Full details of statistical methods, estimations and calculations applied.
- Evidence that the outcomes of the studies have been reviewed and accepted.

NOTE: Actual test results and their acceptance criteria should be provided, and not just pass/fail statements. All data provided should be clearly labeled, and should be clearly linked to the study report. Furthermore, all abbreviations used in reports and on data records should be defined and spelt out in full.

7.6.2. Clinical study - Independent study

The product dossier should contain clinical evidence that demonstrates conformity of the device with the Essential Principles [5] 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

[4] ISO 14155-1:2003

[5] 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.[6]

The WHO Technical Advisory Group on Innovations in Male Circumcision has recommended that the following pivotal clinical studies be conducted independently from the manufacturer in at least two countries representative of the intended use setting.

Clinical study _ Phase 1 (randomized controlled trial):
This phase includes a comparative study (at least 100 patients) that compares the performance of the device with a standard surgical procedure in a randomized controlled trial. This trial needs to be performed by surgeons skilled and equipped to offer either method.

Clinical study _ Phase 2 (field study):
This study phase also called field study, is a non-comparative field trial of the device in settings of intended use, with procedures performed by trained mid-level providers (non-physicians). A cohort study of at least 500 patients in each country is enrolled and followed up.

It is anticipated that principal investigators responsible for the independent clinical trials and field studies will provide a detailed full study protocol, the method of data analysis and the full study report directly to WHO (Department of HIV/AIDS). This information will be reviewed by experts and presented to the WHO Technical Advisory Group on Innovations in Male Circumcision (TAG IMC) for their review. The recommendation from the TAG IMC will constitute the information required for this section of the dossier.

Scientifically sound clinical data should include:

- the evaluation study design, study protocol, results, and conclusions;
- the date/s on which the study was performed;
- clear identification of the product and product version that is being evaluated;
- details of the product lots/batches used for the evaluation, including lot number, date of expiry, and the storage conditions of the product prior to and during the study;
- details of the geographical region and the clinical status of the subjects included in the study;
- details of the methods used to define the clinical status of the subjects;
- details of statistical methods, estimations and calculations applied;
- details of the entity which performed the evaluation, including current contact details;
- a declaration from the entity which performed the evaluation declaring any interests that could constitute a real, potential, or apparent conflict of interest with respect to their involvement in the independent study of this product or the manufacturer of the product.

[6] ISO 14155-1:2003

8. Labelling

The product dossier should typically contain a complete set of labelling associated with the product. Information on labelling should include the following:

- packaging labels
- instructions for use
- any other instructional materials provided to the user or patient.

NOTE: Labelling information in the product dossier is provided in English. The manufacturer should ensure that translations into other languages are accurate and of good quality. A poor quality translation may severely compromise the safety and performance of the male circumcision device. Translations should be made by qualified medical translators and should be double checked by the manufacturer or the translation office.

8.1. Labels

Include copies of all the packaging labels for the product - include outer package labels and also component labels, where applicable.

The label should contain the following particulars which may appear on the device itself, or on the packaging of each unit, or on the packaging of multiple devices.

1. The name or trade name of the medical device.
2. The details strictly necessary for a user to identify the device and its use, e.g. 'male circumcision device', and a product (catalogue) code.
3. The name and address of the manufacturer in a format that is recognisable and allows the location of the manufacturer to be established [7].
4. For imported devices, the name and postal address of the authorised representative, or importer or distributor established within the importing country/jurisdiction may be required. This information may be added by the authorised representative, importer, or distributor within the country of import, rather than be provided by the manufacturer, in which case, the additional label should not obscure any of the manufacturer's labels.
5. Where appropriate, an indication that the device contains or incorporates a medicinal or biological substance.
6. The batch code/lot number or the serial number of the device preceded by the word LOT or SERIAL NUMBER or an equivalent symbol, as appropriate, to allow post-market action to be taken if there is a need to trace or recall the device.
7. An unambiguous indication of the date until when the device may be used safely, expressed at least as the year and month (e.g. on devices supplied sterile or single use disposable devices), where this is relevant.
8. Where there is no indication of the date until when it may be used safely, the year of manufacture. This year of manufacture may be included as part of the batch or serial number, provided the date is clearly identifiable.
9. An indication of any special storage and/or handling condition that applies.

[7] An abbreviated version of the address may be sufficient on the label if the device is accompanied by instructions for use that provide a full address.

10. If the device is supplied sterile, an indication of its sterile state and, where appropriate, the sterilization method.
11. Warnings or precautions to be taken that need to be brought to the immediate attention of the user of the medical device as relevant, and to any other person where appropriate (e.g. 'THIS PRODUCT CONTAINS LATEX'). This information may be kept to a minimum in which case more detailed information should appear in the instructions for use.
12. If the device is intended for single use, an indication of that fact.

8.2. Instructions for use

A copy of the current instructions for use should be included. If at the application form stage the manufacturer has been required to address any issues related to the instructions for use, the amended instructions for use should be submitted as part of the dossier. The instructions for use will be reviewed for clarity, correctness, and suitability for the target user group. The instructions for use should contain the following particulars:

1. The name or trade name of the medical device.
2. The name and address of the manufacturer in a format that is recognisable and allows the location of the manufacturer to be established, together with a telephone number and/or fax number and/or website address to obtain technical assistance.
3. The device's intended use/purpose including the intended user (e.g. professional or lay person), as appropriate, and patient population.
4. The performance of the device intended by the manufacturer.
5. Where the manufacturer has included clinical studies as part of premarket conformity assessment to demonstrate conformity to Essential Principles, a summary of the investigation, outcome data and clinical safety information, or a reference as to where such information may be accessed.
6. Any residual risks, contraindications and any expected and foreseeable side effects, including information to be conveyed to the patient in this regard.
7. Specifications the user requires to use the device appropriately, e.g. if the device has a measuring function, the degree of accuracy claimed for it.
8. If the device contains, or incorporates, a medicinal substance and/or material of biological origin, identification of that substance or material, as appropriate.
9. Details of any preparatory treatment or handling of the device before it is ready for use (e.g. sterilization, final assembly, calibration, etc.).
10. Any requirements for special facilities, or special training, or particular qualifications of the device user and/or third parties.
11. The information needed to verify whether the device is properly installed and is ready to perform safely and as intended by the manufacturer, together with, where relevant:
    - details of the nature, and frequency, of preventative and regular maintenance, and of any preparatory cleaning or disinfection;
    - identification of any consumable components and how to replace them;
    - information on any necessary calibration to ensure that the device operates properly and safely during its intended life span**;**
    - methods of eliminating the risks encountered by persons involved in installing, calibrating or servicing medical devices.
12. An indication of any special storage and/or handling condition that applies.
    If the device is supplied sterile, instructions in the event of the sterile packaging being

damaged before use.

13. If the device is supplied non-sterile with the intention that it is sterilized before use, the appropriate instructions for sterilization.
14. If the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of re-sterilization. Information should be provided to identify when the device should no longer be reused, e.g. signs of material degradation or the maximum number of allowable reuses.
15. For devices intended for use together with other medical devices and/or general purpose equipment:
    - information to identify such devices or equipment, in order to obtain a safe combination, and/or
    - information on any known restrictions to combinations of medical devices and equipment.
16. If the device emits hazardous, or potentially hazardous levels of radiation for medical purposes:
    - detailed information as to the nature, type and where appropriate, the intensity and distribution of the emitted radiation;
    - the means of protecting the patient, user, or third party from unintended radiation during use of the device;
17. Information that allows the user and/or patient to be informed of any warnings, precautions, measures to be taken and limitations of use regarding the device. This information should cover, where appropriate:
    - warnings, precautions and/or measures to be taken in the event of malfunction of the device or changes in its performance that may affect safety;
    - warnings, precautions and/or measures to be taken with regard to the exposure to reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, radiation associated with diagnostic or therapeutic procedures, pressure, humidity, or temperature;
    - warnings, precautions and/or measures to be taken with regard to the risks of interference posed by the reasonably foreseeable presence of the device during specific diagnostic investigations, evaluations, therapeutic treatment or use (e.g. electromagnetic interference emitted by the device affecting other equipment);
    - if the device administers medicinal or biological products, any limitations or incompatibility in the choice of substances to be delivered;
    - warnings, precautions and/or limitations related to the medicinal substance or biological material that is incorporated into the device as an integral part of the device;
    - precautions related to materials incorporated into the device that are carcinogenic, mutagenic or toxic, or could result in sensitisation or allergic reaction of the patient or user.
18. Warnings or precautions to be taken related to the disposal of the device, its accessories and the consumables used with it, if any. This information should cover, where appropriate:
    - infection or microbial hazards (e.g. explants, needles or surgical equipment contaminated with potentially infectious substances of human origin);
    - environmental hazards (e.g. batteries or materials that emit potentially hazardous levels of radiation);
    - physical hazards (e.g. from sharps).
19. For devices intended for use by lay persons, the circumstances when the user should consult

with a healthcare professional.

20. Any information or instructions to be given to the patient including any required follow-up procedures, for example for device removal if the device is intended to remain on the penis for an extended period, and the circumstances when the patient should consult with a health care professional.
21. Date of issue or latest revision of the instructions for use and, where appropriate, an identification number.

In addition, provide copies of any other instructional materials that are provided to the user.

9. Commercial History

9.1. Countries of supply

The information provided in this section should include:

- A list all countries in which the product under assessment is currently supplied and the year when supply started. This includes all countries where the device has been made available, in return for payment or free-of-charge, for distribution and/or use in that country.
- Detailed information about the training and support network that is available in each country of supply. For example:
  a) how the users are trained in the operation of the device;
  b) how the users of the product contact the supplier/manufacturer for technical support;
  c) if there are representatives located in each country of supply to provide technical support; and
  d) how many representatives are available in each country of supply to provide technical support.
- The minimum and maximum price of supply for this product for the last financial year, if available. These prices should be the global minimum and maximum prices and should be quoted in US dollars.
- The number of products sold in each country of supply for the last five financial years, where applicable.

9.2. Adverse events and field safety corrective actions

This section should provide the following information:

- A list of all adverse events that have occurred (within the last five years) that did affect, or could have potentially affected, the performance of the device, safety of the patient, safety of users, or safety of any person associated with this product. Include details of the corrective and preventative action taken.

- A list of all events (within the last five years) that required field safety corrective action such as:
  a) withdrawal of products from sale or distribution
  b) physical return of the product to the manufacturer
  c) product exchange
  d) destruction of the product
  e) product modification/s
  f) additional advice provision to customers to ensure that the product continues to function as intended.

10. Regulatory History

A "National Regulatory Authority" (sometimes also called a Competent Authority) is an entity that exercises the legal right to act on behalf of the Government of a country/region to control the use and supply of male circumcision devices in that country/region.

"Regulatory approval" means that the National Regulatory Authority officially permits supply of this product in the country/region under its authority.

"Type of regulatory approval" refers to the relevant sections of legislation that have been applied to the product for regulatory approval. Generally the details of the legislation applied for regulatory approval should be included on the certificate that demonstrates that the product is approved for supply.

For the male circumcision device under assessment include:

- A list of National Regulatory Authorities which have provided current regulatory approval for the supply of this product in their country/region of authority.
- Details of the type of regulatory approval obtained from each National Regulatory Authority (this refers to the relevant sections of the legislation that have been applied to the product for regulatory approval).
- Current evidence of this regulatory approval, such as certificates provided by the National Regulatory Authority. The evidence should clearly show that the product under assessment falls within the scope of the submitted regulatory approval.
- Details regarding any situations where this product was rejected by a National Regulatory Authority, situations where an application for regulatory approval was withdrawn, or situations where regulatory approval has been withdrawn.

NOTE: Information relating to export-only regulatory approvals should be clearly identifiable as export-only approvals.

11. Quality Management System

An effective quality management system is a key consideration for all manufacturers of male circumcision devices. Therefore, male circumcision devices submitted for prequalification assessment should be manufactured under an appropriate quality management system. The manufacturer's quality management system should cover all sites used to manufacture this product.

The quality management standard *ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes* is considered to be a benchmark in quality management for manufacturers of male circumcision devices by regulatory authorities throughout the world. WHO bases their prequalification of male circumcision devices assessment and inspection processes on the requirements of this internationally recognized quality management

standard.

11.1. Quality manual

Include a copy of the current version of the manufacturer's quality manual [8]. The following aspects should be covered (or referred to) in the quality manual [9]:

- the title and scope
- the table of contents
- the review, approval and revision
- the quality policy and objectives
- the organization, responsibility and authority
- the references
- the quality management system description and
- the appendices.

Include the organizational chart of the manufacturer (if not already available within the quality manual) and document control information for the quality manual (such as version number, release date and approval record).

A complete list of all quality management system documents, with the document title and document number, relevant to this product should be included.

11.2. Quality management system documents

It is expected that, to maintain an effective quality management system for the manufacture of this male circumcision device, the manufacturer will utilize a number of documented procedures. Provide copies of the following documented procedures applied in the manufacture of this male circumcision device:

- The manufacturer's documented procedure/s, relevant to this product, for the control of design and development changes.
- The manufacturer's documented procedure/s, relevant to this product, for the provision of advisory notices to customers subsequent to product delivery.
- The manufacturer's documented procedure/s for corrective and preventative actions for non-conformities relating to the product under assessment.
- The manufacturer's documented procedure/s for batch release.
- The manufacturer's documented procedure/s for the evaluation of key suppliers.
- The manufacturer's documented procedure/s for the quality control of received supplies (ingredients, components).

11.3. Quality management system certification

If the manufacturer holds *ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes* certification for the manufacture of the product under

[8] The manufacturer's quality manual is expected not to exceed 30 pages. However, if it does, please provide only the electronic copy (CD or DVD) of the document.

[9] These requirements are based on the ISO/TR 10013:2001 Guidelines for quality management system documentation. For further information see the following website: www.iso.org

assessment, then provide evidence, such as certified copies of the certificates issued by the Conformity Assessment Body. Ensure that any certificates provided clearly demonstrate that the manufacture of the product under assessment is within the scope of the certification.

12. Contact Information

Any inquiries regarding the prequalification of male circumcision devices should be addressed to: *diagnostics@who.int*

13. Reference Documents

- ISO 13485:2003 *Medical devices - Quality management systems - Requirements for regulatory purposes* [International Organization for Standardization (ISO) document; www.iso.org]
- ISO/TR 10013:2001 *Guidelines for quality management system documentation* [International Organization for Standardization (ISO) document; www.iso.org]
- ISO 14971:2007 Medical devices - Application of risk management to medical devices
- ISO 14155-1:2003 Clinical Investigation of Medical Devices for Human Subjects - General Requirements
- ISO 14155-2:2003 Clinical Investigation of Medical Devices for Human Subject - Clinical Investigation Plan
- GHTF/SG1/N41R9:2005 *Essential Principles of Safety and Performance of Medical Devices* [Global Harmonization Task Force (GHTF) document; www.ghtf.org]
- GHTF/SG1/N70:2011 *Label and Instructions for Use for Medical Devices* [Global Harmonization Task Force (GHTF) document; www.ghtf.org]
- GHTF/SG2/N54R8:2006 *Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices* [Global Harmonization Task Force (GHTF) document; www.ghtf.org]
- GHTF/SG2/N57R8:2006 *Medical Devices Post Market Surveillance: Content of Field Safety Notices* [Global Harmonization Task Force (GHTF) document; www.ghtf.org]
- GHTF/SG5/N3:2010: Clinical investigations [Global Harmonization Task Force (GHTF) document; www.ghtf.org]
- GHTF/SG5/N2R8:2007: Clinical evaluation [Global Harmonization Task Force (GHTF) document; www.ghtf.org]

14. Annex A - Essential Principles (EP) checklist

The EP checklist can be used by manufacturers to readily understand how the manufacturer demonstrates compliance to the Essential Principles for a particular male circumcision device. The EP checklist also allows easy identification of relevant documents and data for conformity assessment purposes.

The following is a recommended template for the EP checklist. Preparation of the EP checklist as outlined below will provide a useful overview of the manufacturer's conformity to the Essential Principles.

14.1. How to fill in the checklist

14.1.1. Identity of the male circumcision device
The manufacturer should identify the male circumcision device, and when applicable the various configurations/variants covered by the checklist.

14.1.2. Applicable to device?
Is the listed Essential Principle applicable to the male circumcision device? Here the answer is either 'Yes' or 'No'. If the answer is 'No' this should be briefly explained.

14.1.3. Method used to demonstrate conformity
In this column, the manufacturer should state the type(s) of method(s) that it has chosen to demonstrate conformity e.g. the recognised standard(s), industry or in-house test method(s), comparison study(ies) or other method used.

14.1.4. Method reference
After having stated the method in the previous column, here the manufacturer should name the title and reference the recognised standard(s), industry or in-house test method(s), comparison study(ies) or other method used to demonstrate conformity. For standards, this should include the date of the standard and where appropriate, the clause(s) that demonstrates conformity with the relevant EP.

14.1.5. Reference to Supporting controlled documents
This column should contain the reference to the actual technical documentation that demonstrates conformity to the Essential Principle, i.e. the certificates, test reports, study reports or other documents that resulted from the method used to demonstrate conformity and its location within the dossier.

NOTE: The table that follows is for illustrative purposes only. The Essential Principles listed in the first column should be extracted from the latest version of the GHTF's guidance document *Essential principles of Safety and Performance of Medical Devices".* Those incorporated into this document are extracted from GHTF/SG1/N41:2005.

Essential Principles Checklist	
Identity of the male circumcision device:	

Essential Principle	Applicable to the device?	Method Used to Demonstrate Conformity	Method Reference	Reference to Supporting Controlled Documents
General Requirements				
5.1 Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.				
5.2 The solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, the manufacturer should control the risk(s) so that the residual risk(s) associated with each hazard is judged acceptable. The manufacturer should apply the following principles in the priority order listed: ▪ identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse, ▪ eliminate risks as far as reasonably practicable through inherently safe design and manufacture, ▪ reduce as far as is reasonably practicable the remaining risks by taking adequate protection measures, including alarms, ▪ inform users of any residual risks.				

Essential Principle	Applicable to the device?	Method Used to Demonstrate Conformity	Method Reference	Reference to Supporting Controlled Documents
5.3 Devices should achieve the performance intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions within the scope of the definition of a medical device applicable in each jurisdiction.				
5.4 The characteristics and performances referred to in Clauses 5.1, 5.2 and 5.3 should not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.				
5.5 The devices should be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected under transport and storage conditions (for example, fluctuations of temperature and humidity) taking account of the instructions and information provided by the manufacturer.				
5.6 The benefits must be determined to outweigh any undesirable side effects for the performances intended.				
Design and Manufacturing Requirements				
5.7 Chemical, physical and biological properties				

Essential Principle	Applicable to the device?	Method Used to Demonstrate Conformity	Method Reference	Reference to Supporting Controlled Documents
5.7.1 The devices should be designed and manufactured in such a way as to ensure the characteristics and performance referred to in Clauses 5.1 to 5.6 of the 'General Requirements'. Particular attention should be paid to: ▪ the choice of materials used, particularly as regards toxicity and, where appropriate, flammability, ▪ the compatibility between the materials used and biological tissues, cells, body fluids, and specimens, taking account of the intended purpose of the device, ▪ the choice of materials used should reflect, where appropriate, matters such as hardness, wear and fatigue strength.				
5.7.2 The devices should be designed, manufactured and packed in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to patients, taking account of the intended purpose of the product. Particular attention should be paid to tissues exposed and to the duration and frequency of exposure.				
5.7.3 ---------- etc. ----------				
5.7.4 ---------- etc. ----------				
5.7.5				
5.7.6				