Information for Manufacturers on Inspections

Prequalification of Male Circumcision Devices

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World Health Organization

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World Health Organization

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 and scope

2.1. Intended audience of this document

This document has been prepared to provide an overview of the inspection component of the WHO prequalification of Male Circumcision Devices. In addition, this document is issued to inspection team members.

2.2. Scope of this document

This document describes the application of internationally recognized standards to the prequalification inspection process facilitated by a WHO lead inspector and conducted with selected quality management system and technical inspectors.

This document is guided by standards and technical reports prepared by the International Organization for Standardization (ISO) and guidelines from the Global Harmonization Task Force (GHTF). Publications from both of these organizations are prepared by recognized experts and are referred to by regulatory agencies throughout the world including the European Community (EC), the USA Food and Drug Administration (FDA) and others.

The inspection process is based on the referenced standards and guidelines. Although it is not mandatory for manufacturers to use these standards and guidelines, a quality system and manufacturing process that fulfils the requirements of these documents will also comply with WHO prequalification requirements. The manufacturer will be required to indicate which standards were used to establish the quality management system under which the product to be prequalified is manufactured.

As a general overview, the inspection criteria for WHO Prequalification of Male Circumcision Devices Programme inspections are product-specific and are based on an assessment of compliance with 'ISO 13485:2003 Medical devices - Quality management systems - Requirements for regulatory purposes' and 'ISO/TR 14969 Medical devices - Quality management systems - Guidance on the application of ISO 13485:2003.' Additional references relating to best practice for the manufacturing, including other ISO standards, will be utilized. The inspections are based on the principles outlined in ISO 19011:2002 'Guidelines for quality and/or environmental management systems auditing'.

IMPORTANT NOTE: It must be understood that the inspection will not necessarily be limited to this document i.e. ISO13485. The inspection will be conducted to reflect the particular product and best practice for production in the type of manufacturing facility, as appropriate and as determined by the team of inspectors.

This document is to be used with the reference documents listed in Annex 1. More detailed explanation of the topics in this document can be found in the reference documents. In addition, a reference list of definitions can be found in Annex 2.

3. The Inspection Process

3.1. Objectives and scope of the inspection

3.1.1. Objectives of the inspection

The overall intent of the inspection is to ensure the quality of the male circumcision device. Therefore, the specific objectives of the inspection are to ensure compliance of the manufacturer's quality management system and manufacturing practices with international best practice, to determine the effectiveness of the implemented quality management system in meeting appropriate quality standards, to inspect the quality management system according to the manufacturer's own requirements and to confirm the content of the submitted dossier.

3.1.2. Scope of the inspection

The scope of the inspection is limited to the agreed upon location and product. The inspection will include all organizational units, activities and processes associated with the product. The inspection team will review documents related to the quality management system and manufacture of the product to be prequalified, including standard operating procedures and records. These documents are to be readily available at the time of the inspection.

Inspections are performed in a sample audit format. That is, not all details of the manufacturing process will be examined. However, the expertise of the inspectors will guide them in selecting those processes that are indicative of producing a device of high quality.

The inspection will be limited to the allocated time. If critical nonconformities are identified, further inspections may be considered necessary after discussion with the inspectors and the manufacturer.

IMPORTANT NOTE: The site of manufacture must be in active production at the time of the inspection for the inspection team to perform an adequate assessment. The scheduling of the inspection must therefore coincide with production of the device to be prequalified. In addition, key personnel must be present at the time of the inspection.

3.2. Principles relating to the inspection

The following items are to be considered guiding principles governing the inspections:

- Independence
  The inspectors that include WHO staff and selected regulatory and technical inspectors shall be impartial and free from influences that could affect their objectivity.
- Inspection objectives and scope

The inspection objectives and scope shall be defined in a general audit plan provided to the manufacturer and agreed upon with the manufacturer prior to the inspection. Modification to this may be required, depending on the observations made at the time of the inspection.

- Roles and responsibilities
  Roles and responsibilities of all personnel involved in the inspection shall be clearly defined so that expectations can be met and accountabilities are understood.
- Resources
  Resources shall be adequate in terms of competent inspectors, expertise as deemed necessary, time allocation and access to external technical and other information. The resources utilized shall ensure that the inspection results are highly reliable.
- Competence of the inspection team
  The inspection team shall consist of inspectors with auditing skills and with the education and experience in regulatory requirements and device technologies appropriate for their tasks during the inspection.
- Consistency of procedures
  The inspection procedure shall be performed according to defined guidelines and with a WHO officer as team leader to ensure consistency between inspections of the same type and scope.
- Adequacy of inspection documentation
  Documentation associated with each inspection shall provide adequate information to be used for pre-approval and post-approval surveillance of the product, for continuity between successive inspections and to provide opportunities for quality improvement to the manufacturer.
- Confidentiality and standard of conduct
  The inspectors shall maintain confidentiality with regard to information and documentation related to the inspection and comply with the defined WHO standards of conduct. Within these considerations, the inspection process is to be transparent to all participants.
- Inspection results and conclusions
  The results and conclusions of the inspections shall be consistent and accurate subject to the normal limitations of an inspection, noting that the objective evidence collected during the inspection is generally a sample.
- Quality system
  Inspections are conducted within the prescribed WHO internal quality management system.

3.3. Types of inspections

The four types of inspection that are possible are outlined in this section.

3.3.1. Initial inspection

All aspects of the quality system and manufacturing processes will be examined in an initial inspection. A follow-up inspection to confirm correction of nonconformities may be required as part of the initial inspection.

3.3.2. Surveillance inspection

This is a partial inspection and will be scheduled based on risk assessment criteria. It is usual that one or two surveillance inspections will occur between the initial and reassessment inspections.

3.3.3. Reassessment inspection

This will either be a partial or full inspection depending on, for example, the results of the previous WHO inspection, the type of product, results of inspections by other agencies, recalls or complaints since the last inspection, results of product testing and any other relevant changes or information.

3.3.4. Special inspection

This may be required when, for example,

- significant changes are made to the product for which the manufacturer has been granted prequalification (e.g. changes to the device format, manufacturing methods, facilities or changes to other relevant production aspects)
- serious concerns have been raised about the ongoing quality of the device
- production has been suspended and then recommenced
- there is a significant change in management structure

3.3.5. Waiver of site visit.

A site visit may be waived under exceptional circumstances such as recent inspection by a WHO recognized inspection agency and the full report and other requested documentation being made freely available to WHO inspection staff for review.

3.4. Roles and responsibilities

The inspection team leader is generally a WHO employee who has responsibility for all phases of the inspection and has authority to make final decisions regarding conduct of the inspection and observations made during the inspection.

3.4.1. Responsibilities of the WHO inspection team leader

Responsibilities of the WHO inspection team leader are in addition to those of an inspector, described below. The WHO inspection team leader's responsibilities are to:

- assist with the selection of the inspection team members
- supervise inspectors during the inspection
- define the scope of the inspection
- initially review the summary dossier report on the manufacturer's submitted dossier
- prepare the inspection plan, working documents, briefing documents and supervise the travel arrangements for the inspectors
- represent the inspection team with the manufacturer

- communicate any obstacles regarding the inspection to the manufacturer and to the WHO prequalification team prior to or during the inspection
- prepare and present the inspection general outcome, after consultation with the other inspectors, to the manufacturer at the closing meeting
- prepare and submit the final inspection report in a timely manner (usually within two months), after consultation with the other inspectors, for review and approval by the programme coordinator
- submit the report to the manufacturer

3.4.2. Responsibilities of the inspectors

Each inspector's responsibilities are to:

- use established inspection methods to ensure consistency in the inspection process
- plan and carry out assigned responsibilities objectively, effectively and efficiently within the inspection scope
- safeguard confidentiality of documents and information in association with the inspection
- ensure compliance with the WHO standard of conduct
- ensure compliance with the WHO prequalification of devices requirements for inspections including information in this document
- assist the manufacturers to understand the WHO prequalification requirements
- collect, analyse and document objective evidence to establish the extent of compliance with the quality system and the effectiveness of its implementation
- establish the extent to which the procedures, documents and other available information is understood and used by the manufacturer's personnel
- cooperate with and support the inspection team leader and maintain a means of obtaining prompt guidance during the inspection if required
- bring to the attention of the inspection team leader in a timely manner, any indications or observations that could influence the inspection results, require more in depth inspection or are an obstacle to the proper performance of the inspection
- when applicable, verify corrective actions have been taken and have been effective
- minimize disruption to the manufacturer's personnel and processes during the inspection and comply with any health and safety or other requirements of the manufacturer
- perform the inspection to achieve the objectives in a polite and enquiring manner without discourteous or intimidating conduct
- assist the inspection team leader in preparing the report of the inspection

Note: All notes and other documented evidence gathered at the inspection will form part of the WHO records of the inspection.

3.4.3. Responsibilities of the manufacturer

Responsibilities of the manufacturer are communicated to the manufacturer prior to the inspection. According to these, the manufacturer's responsibilities are to:

- define and agree upon the objective and the scope of the inspection with the WHO prequalification team
- inform the prequalification team of any issues that may affect an effective and efficient inspection process
- cooperate with the inspectors to ensure that the inspection objectives are achieved
- identify a person responsible for coordinating and facilitating the inspection process
- inform relevant employees about the objectives and the scope of the inspection
- appoint responsible members of staff to accompany members of the inspection team and to ensure inspectors are aware of health, safety and other applicable requirements
- provide on-site resources, such as a meeting room, for the inspection team to ensure an effective and efficient inspection process
- provide access to the manufacturing facilities, documents and records and other evidence as requested by the inspectors in a timely manner to ensure an effective and efficient inspection process and so that the inspection timetable can be met

In addition, subsequent to receiving the inspection observations at the exit meeting and the completed inspection report, and if nonconformities are identified, the manufacturer's responsibilities are to:

- determine the root cause of nonconformities identified
- determine the corrective actions to be taken to address the nonconformities and to correcting directly related and / or related systemic issues
- implement and verify the effectiveness of the corrective actions in a timely manner
- inform WHO of these actions as required by the final report
- inform WHO of any subsequent significant quality system changes
- inform all those personnel that may be affected about the results of the inspection

3.5. Inspection team selection

3.5.1. Composition of the inspection team.

The inspection team may consist of:

- the inspection team leader who is generally a member of the WHO secretariat
- a technical inspector who is knowledgeable and experienced in assessing the relevant device that includes the manufacturing process and resultant product (more than one person may be required).
- a quality management systems inspector qualified and experienced to inspect the quality management system of the type of manufacturer being inspected (this role may be performed by the WHO inspection team leader or by a suitably qualified technical auditor)
- an inspector expert in quality control activities including the on-site laboratory responsible for activities such as batch release testing
- inspectors from local National Regulatory Authorities
- observers that can include personnel from other inspection agencies, and inspection trainees. The observers are not considered to be inspectors but must comply with the

same standards of conduct as the inspectors. The number of observers must be limited to ensure minimal disruption to the inspection and to the manufacturing process.

Note: inspectors may fulfill multiple roles.

The manufacturer will be informed of the identity of the proposed inspectors and observers prior to the site inspection and receive their curriculum vitae to ensure there are no conflicts of interest or other issues that may compromise the inspection. The manufacturer has the opportunity to express concerns to WHO regarding any of the inspectors before the visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer may object to a team member's participation in the site visit within 10 days of receipt of the proposed inspection team composition.

3.5.2. Standard of conduct

All members of the inspection team and all observers must be made aware of and agree to the high standard of conduct expected during the entire inspection process, including pre- and post-inspection activities, and confidentiality and absence of conflict of interest. The conduct required is in keeping with the requirements of the WHO International Civil Service Commission 'Standards of Conduct for the International Civil Service'.

3.6. Dossier review summary report

As part of the WHO Prequalification of Male Circumcision Devices Programme, an application form and dossier are submitted to WHO in accordance with specified requirements. A dossier review summary report is prepared by WHO dossier assessors and submitted to the lead inspector. When the lead inspector is satisfied that the summary dossier review report is complete (see below), the quality and technical inspectors then view the report in preparation for the on-site inspection. Other documentation reviewed may include previous inspection reports. Issues arising from these reports are noted. Any other relevant documentation or information is made available to all of the participating inspectors for review.

3.7. Logistics, documentation and travel for inspection

3.7.1. Dates and time allocated for inspection

The dates and time allocated for the inspection are to be agreed upon by all participants under the guidance of the inspection team leader and will be documented in an inspection plan.

The manufacturer will be asked to accept the proposed dates for the inspection when:

- the production line of the product to be prequalified is active
- quality control activities are being performed
- the key personnel for the quality management system, quality control and production line will be present

The inspection plan will be provided usually one to two weeks before the inspection and will include an overview of the type of audit to be conducted using information from the submitted

dossier, which includes the quality manual. The plan is a guide only and will be flexible to permit changes in emphasis based on information gathered during the inspection.

The inspection plan will include:

- the inspection scope and purpose
- identification of inspection team members
- identification of the contact person representing the manufacturer for the inspection
- date and place of inspection, expected time and duration of each inspection activity including meetings to be held with the manufacturer's management team

Time allocated and the inspection plan will vary according to the complexity of the scope of the inspection. A sample of an inspection plan is provided in Annex 3. Inspectors will be allocated tasks by the inspection team leader according to their expertise and the requirements of the inspection.

3.7.2. Documentation regarding subcontractors

The manufacturer must have the necessary documentation available to demonstrate that subcontractors, such as providers of components used to make the device, meet relevant quality expectations. Inspection of subcontractor sites may be necessary if this requirement is not adequately fulfilled.

3.7.3. Working documents for on-site inspection

Inspectors will be provided with an aide memoire appropriate to their area of inspection. The aide memoires do not necessarily define the entire scope of the inspection. Additional items may be included according to the particular requirements of the device and the expertise of the inspector.

It is expected that inspectors will document their findings as the inspection progresses. This information will be used by the inspection team leader to compile the onsite report and subsequent final report and form part of the inspection records.

3.7.4. Language for the on-site inspection

The inspection will be conducted in English. It would be appreciated if the manufacturer could make available key documents that include an English translation. Interpreter requirements will be discussed with the manufacturer prior to the inspection.

3.7.5. Travel and accommodation arrangements

The inspection team leader has the responsibility for the organization of the travel and accommodation requirements for the inspection team. This responsibility will not extend to the observers except under particular circumstances. The manufacturer will generally be asked to use their local knowledge to assist with local travel and accommodation arrangements.

4. The Inspection Onsite

4.1. Opening meeting

The preliminary meeting (1 hour total) is held to exchange information between the inspection team and the manufacturing team on the inspection process and manufacturing site. The times indicated below may act as a guide.

4.1.1. Inspection team (20 minutes)

The inspection team will first:

- introduce inspection team members
- review scope and objectives of inspection
- provide a short summary of the inspection process and confirm the timetable
- establish official communications links between the manufacturer and the inspection team for the duration of the inspection
- confirm that the resources and facilities needed by the inspection team are available
- allow manufacturer to ask clarifying questions regarding the process

4.1.2. Manufacturer (40 minutes)

Then, the manufacturer will:

- introduce principle staff - provision of an organigram and a written list with contact details would facilitate access to key personnel during the inspection process
- provide brief overview of on site manufacturing process particularly for the product to be prequalified
- provide brief overview of the quality management system
- inform the inspection team of any changes since the submission of the dossier

4.2. The inspection

4.2.1. General

The inspection will seek to confirm the adequacy and effectiveness of the Quality Management System (QMS) including the technical / production process and that it represents best practice and includes the correct implementation of the manufacturer's documented procedures. The inspection will be process based on the Plan, Do, Check Act model (refer Annex 6).

Documents from all levels of the quality system will be reviewed. Post-market surveillance data may be included in the review.

Informal questioning of personnel at all levels and with persons selected by an inspector will form part of the inspection process.

Evidence will be collected on-site, as follows:

- by examination of documents including standard operating procedures and records
- by visual observation of activities
- by visual observation of conditions
- confirmation of statement of fact that is acquired through interviews
- may include random sampling of product for laboratory testing
- may include photographs

Nonconformities may be verified by acquiring additional information when possible. The manufacturer will be given an immediate opportunity to comment on the evidence of nonconformities. Based on this evidence, a nonconformity, even if corrected immediately, will be noted and form part of the onsite and final inspection report.

4.2.2. Quality management system inspection overview

The QMS inspection will be conducted in a format that follows the production process. The numbers in brackets below indicate the area of ISO 13485:2003 that is relevant to this process. Note that this standard is used as a basis for the inspection and that other standards and references may be used by the manufacturer to ensure best practice in the manufacture of the devices.

The QMS inspection process includes but is not limited to:

- management (4 - 8): inspection of management processes is to ensure that an adequate and effective quality management system is in place, including management review
- product documentation (4,7) including design and development: inspection of this section is to ensure that the manufacturer has sufficient documented systems and adequate communication of the systems (including change control) to all personnel, to ensure a quality product outcome
- production and process controls (4,6,7,8): inspection of this section is to ensure that the manufacturer has sufficient systems such as testing, infrastructure, facilities, equipment and personnel to ensure a quality outcome; demonstrated independence between the production and quality unit and that the quality unit controls release of product batches
- corrective and preventive actions, internal audits, management review (4 - 8): inspection of this section is to confirm that the manufacturer collects and analyses actual and potential quality problems through investigation and appropriate action
- purchasing controls (7): this section is especially important when significant components are outsourced. The manufacturer must ensure that products and services provided by suppliers are of an appropriate standard. Refer 3.7.2 above.
- documentation and records (4): inspection of this section is to ensure that relevant documents and records are controlled, for example, by being updated and properly authorized; and to ensure procedure and process documents are readily available and in routine use by staff as needed

- customer related processes (7): customers in this context include purchasers and users of the product and relevant regulatory bodies
- training of personnel (6): inspection of this section is to ensure that adequate qualifications and training of personnel appropriate to the tasks required of them; training records
- adequate infrastructure (6): inspection of this section is to ensure the adequacy of facilities, manufacturing, equipment, monitoring and quality control equipment; calibration and maintenance

4.2.3. Technical / production inspection overview

The technical inspection will be conducted in a format that follows the production process. The numbers in brackets indicate the area of ISO 13485:2003 that are relevant to this process.

The technical inspection process includes:

- Planning of product realization (7.1)
- Customer-related processes (7.2)
- Design and development (7.3)
- Purchasing (7.4)
- Production and service provision (7.5)
- Control of monitoring and measuring devices (7.6)

4.3. Meeting of inspectors

Inspectors will meet as necessary throughout the inspection, with the following meetings to take place as a minimum:

- Discussion of findings: During the course of the inspection, the inspectors, under the guidance of the inspection team leader, will confer regularly and informally regarding the progress of the inspection.
- Daily summary: At the conclusion of each day, the team leader will present a brief summary of the day's findings.
- Inspection summary: At the conclusion of the inspection process on the last day of the inspection, the inspectors will meet to discuss their findings in detail.
- Preparation of summary: the inspectors will then assist the inspection team leader in summarizing the outcome of the inspection.

4.4. Closing meeting

4.4.1. Summary and inspection reports

The summary inspection onsite report is a draft consensus report compiled and presented by the inspection team leader at the closing meeting. It will describe the main findings, areas of concern and summarize the general issues relating to the inspection. It will contain specific information on the nonconformity activities observed by the inspectors and may include an indication of their relative severity. The inspectors will be available to provide additional explanation if required.

The summary onsite report will allow the manufacturer to begin any corrective actions required immediately. A time frame for the implementation of corrective actions should be agreed to if possible at the closing meeting or will be indicated in the final inspection report.

4.4.2. Comment

The manufacturer's management team will have an opportunity to comment on and to seek clarification on items in the summary report from the inspection team. The inspection team leader will have the final decision on the content of the summary and inspection reports.

5. Inspection Reporting

5.1. Overview

The purpose of the final inspection report is to:

- provide the manufacturer with information on nonconformities found at the inspection that must be addressed to ensure eligibility for WHO prequalification of the device.
- provide information to the manufacturer on which to base improvements to the quality of the manufacturing system.
- provide the WHO team with a permanent record of the findings of the inspection.

A more detailed list of the purpose is found in GHTF/SG4 (pd1)/N33R13:2006 'Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers - Part3: Regulatory Audit Reports and ISO 19011:2002 'Guidelines for quality and/or environmental management systems auditing'.

The inspection team leader prepares the document and is responsible for its accuracy and content. A draft report is left on site on the final day of the inspection. A final report is available generally within two months of the inspection although this time may be extended during periods of high workload and vacation.

Inspection reports will be broadly of two types, as detailed below.

5.1.1. Reports with no requirements

The inspection report is a consensus report compiled by the inspection team leader. The participating inspectors may be asked to review the report for accuracy. Following approval by the WHO authorized approver, the report is submitted to the manufacturer.

5.1.2. Reports with requirements (relating to nonconformities)

The inspection report is a consensus report compiled by the inspection team leader. Following authorization by the WHO authorized approver, the report is submitted to the manufacturer. It includes a description of the nonconformities found during the inspection, and their severity. Nonconformities and observations require a written response and may require evidence of the corrective actions taken.

The response from the manufacturer, initially in the form of an action plan, is generally required within one month of receipt of the final report and the request from the lead inspector. The period required to address nonconformities is required in the action plan.

The inspection team leader asks for and reviews subsequent submissions from the manufacturer relating to correction of the nonconformities. The inspection team leader may request comment on the adequacy of these from the participating inspectors. Then, one of the following outcomes may occur:

- if the submissions are acceptable, the inspection team leader notifies the manufacturer by letter and notifies the WHO authorized person that the inspection and follow-up are complete
- if the submissions are not acceptable, the inspection team leader may request further evidence that must be presented in a timely manner before finalizing the inspection
- if there are significant nonconformities, either in severity or number, a second site inspection may be required to confirm that corrective actions are adequate. This second confirmatory inspection must be conducted within six months of the initial inspection. If more than six months elapses before the manufacturer provides satisfactory responses, a full inspection will be required.

5.2. Contents of the inspection report

The main components of the inspection report include:

- scope and objective of the inspection including the processes and the product
- details of the WHO inspection team
- details of the areas covered in the inspection
- details of nonconformities (and their relative severity) and date for submission of any corrective actions required
- comment and conclusions about the effectiveness of the manufacturer's quality system in meeting quality objectives
- summary of conclusions
- authorized signature and date of the report

The report includes the following comment: 'This report contains the collective views of the inspection team performing this inspection and does not necessarily represent the decisions or the stated policy of the World Health Organization'.

5.3. Retention of inspection reports

Retention of reports and associated documentation is for the period of 3 consecutive inspections and for 5 years following the last inspection.

5.4. Review of nonconformities

The lead inspector will be responsible for requesting, reviewing and reporting on the manufacturer's responses to nonconformities observed during the inspection.

In general, the manufacturer may have a maximum of three requests to supply the necessary information to address nonconformities in a timely manner, usually within one month of the request. However, the nature of some non conformances may require an extended time period to correct. Consideration may be given to justifiable requests for an extension of time to respond. If the manufacturer fails to respond adequately to requests for submissions relating to nonconformities in the requested timeframe, the process will be terminated and the manufacturer will have the option to reapply for prequalification in 12 months from the date of termination.

5.5. Completion of the inspection

The inspection is complete when the inspection report is issued to the manufacturer. When the requirements regarding the nonconformities have been addressed as requested by the WHO lead inspector and the results accepted, the manufacturer will be informed by letter / email. The lead inspector also notifies the WHO authorized person that the inspection and follow-up are complete

A plan for the next inspection will be made at this time. The period of validity will be determined using a risk management approach after all of the information from the dossier, laboratory evaluation and site inspection are collated.

5.6. Criteria for not recommending prequalification to the WHO-authorized approver

Based on the consensus view of the inspectors and following review by WHO, a product may be recommended not to be prequalified. Criteria for not recommending prequalification may include the following reasons (examples only; not exhaustive):

- failure to maintain an adequate quality system
- falsification of data or submitted evidence or deliberate misrepresentation of facts regarding the manufacturing and quality system
- excessive number of non conformance identified
- failure to implement appropriate action when post market data has identified a pattern of defects
- failure of the product to meet the manufacturer's own specifications
- failure of the manufacturer to respond adequately to requests for submissions relating to nonconformities

5.7. Internal DLT review of the inspection process

An internal review of the inspection process is carried out to ensure high quality of the inspection process. This internal review identifies areas that could be improved:

- in the pre-inspection preparation in terms of increased efficacy, efficiency and economy
- during the inspection and includes a review of the performance of the inspectors
- in the post-inspection process and includes a review of the timely submission of the final report

Opportunities for improvement are identified and are documented in the DLT quality system. Action arising from identifying opportunities for improvement is also documented in the DLT quality system. The inspection team leader is responsible for providing information for this review that is then reviewed by the DLT quality officer and authorized by the DLT coordinator.

Annexes

Annex 1: Reference documents

Note: Standards and other reference documents are constantly being updated. Refer to website or other sources to confirm up to date versions.

Reference documents

International Organization for Standardization (ISO) www.iso.ch including but not limited to:

- ISO 13485:2003 'Medical devices - Quality management systems - Requirements for regulatory purposes'
- ISO 14969:2004 'Medical devices - Quality management systems - Guidance on the application of ISO 13485:2003'
- ISO 19011:2011 Guidelines for quality and/or environmental management systems auditing.
- ISO 14971:2007 Medical devices - Application of risk management to medical devices
- ISO 9000:2005 Quality management systems - Fundamentals and vocabulary
- ISO 14644: 1999-2005 Cleanrooms and associated controlled environments (parts 1-5)

Global Harmonization Task Force (GHTF) www.ghtf.org including but not limited to:

- GHTF/SG4/N28R4:2008 'Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers - Part 1: General Requirements' (including supplements 1,2, 4 and 6). Note: 10.2.1 and 10.2.3 in this document further describe audit team competency criteria.
- GHTF/SG4/N30R20:2006 'Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers - Part 2: Regulatory Auditing Strategy'
- GHTF/SG4/N33R16:2007 'Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers - Part 3: Regulatory Audit Reports'

Other:
Relevant harmonized European Directives.

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Annex 2: Definitions

The list of definitions below is based on GHTF.SG4. (99)28 'Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers - Part1: General Requirements.

Note: The words audit and inspection are considered here to be equivalent.

Definitions:

- audit / inspection - a systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives [ISO 8402].
- auditor / inspector - a person with relevant qualifications and competence to perform audits or specified parts of such audits and who belongs to, or is authorized by, the auditing / inspection organization.
- inspection team leader - an inspector designated to manage an inspection
- manufacturer - the legal entity subject by regulation to quality system requirements.
  Note: In several international standards the term 'supplier' is substituted for the term 'manufacturer'.
- nonconformity - the non fulfilment of specified requirements within the planned arrangements.
  Note: Other terms may be used to mean the same as nonconformity (e.g. 'noncompliance', 'non conformance'). Nonconformity is considered equivalent and is used in this document.
- objective evidence - verifiable information or records pertaining to the quality of an item or service or to the existence and implementation of a quality system element, which is based on visual observation, measurement or test.
- quality audit / inspection observation - statement of fact made during a quality audit and substantiated by objective evidence.
- quality system - the organizational structure, responsibilities, procedures, processes and resources for implementing quality management [ISO 8402].
  Note: For the purpose of this information document 'implementing quality management' is taken to include both the establishment and maintenance of the system.
- subcontractor - an entity, separate from the manufacturer, that provides to the manufacturer either a material, product or sub-assembly (or a component) to a proprietary specification which is incorporated into or used in the manufacture of the finished medical device or a service (e.g. testing, sterilization) to enable the medical device to meet defined requirements. If the separate entity is owned by the manufacturer, it may or may not be considered a subcontractor, depending upon the control exercised by the manufacturer.

Annex 3: Example of inspection time table

Example of a time table of an inspection of a manufacturing site. Times may be modified to better comply with the daily production routine. Length of the site visit will vary according to inspection requirements.

	Time	Inspection Activity
Day 1	9.00 - 10.00	Opening meeting Introduction of personnel and overview of inspection by WHO lead inspector; overview of manufacturing process, principle staff and quality system from manufacturer.
	10.00 - 12.30	Inspection (includes 15 minute break) Quality System: Management responsibility (5) including interviewing of senior management. Planning of product realization (7.1), Customer-related processes (7.2), Design and development (7.3), Purchasing (7.4) Quality System: Quality management system (4). Production and service provision (7.5), Control of monitoring and measuring devices (7.6)
	12.30 - 13.15	Break
	13.45 - 17.00	Inspection (continued) Quality System: Resource management (6), Measurement Analysis & improvement (8)
	16.45-17.00	Inspectors report briefly to manufacturers on day's findings
Days 2-3	All day	Inspection continued as above and as required.
Final day	9.00 - 12.30	Inspection (continued)
	12.30 - 13.15	Break
	13.15 - 16.00	Inspectors meeting: discuss findings, prepare summary report
	16.00 - 17.00	Closing meeting: present inspection outcome and summary report and discuss findings with manufacturer

World Health Organization

Annex 4: Internet resources

The resources listed below are available on the internet. This resource list is provided to assist manufacturers in preparation for a WHO prequalification inspection. This list is not intended to be exhaustive and manufacturers can access any sources that will assist them in preparation for a WHO prequalification inspection.

This list includes comment on the importance and relevance of the documents and reference to the manufacturing elements that will be the focus of the prequalification inspection.

World Wide Web (www.) resources - no cost

Global Harmonization Task Force (GHTF)
www.ghtf.org
This is a useful site due to the relevance of the documents and the quality of the input in the preparation of the documents. Documents on this site (Study Groups 1 to 5) were created by a volunteer group of international regulatory experts from the US Food and Drug Administration (FDA), Australian Therapeutic Goods Administration (TGA), Japanese Ministry of Health, Labour and Welfare, Health Canada, Medical Devices Bureau, representatives from Europe - Notified Bodies, and included experts from industry in these countries together with contributors from other countries. The documents relate to ISO 13485:2003 and US FDA 21 CFR Part 820 and other GHTF guidance documents, ISO standards and technical reports and to FDA documents as applicable.

US Food and Drug Administration (FDA) 'Guide to Inspections of Quality Systems'
http://www.fda.gov/ora/inspect_ref/igs/qsit/QSITGUIDE.HTM#page33
A useful guide written for FDA field staff who perform quality system inspections. It provides a good description of the elements involved. The FDA site has many other publications freely available.

Other World Wide Web resources - with cost

International Organization for Standardization (ISO)
http://www.iso.ch
Follow link 11. 'Health care technology'

Link to full list of medical device standards and technical reports
http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=40&ICS3=1&scopelist=
The two important standards pertaining to the manufacture of medical devices are 13485:2003 and 14969:2004. These can be bought and downloaded online from this site.
There are other relevant standards and technical reports as listed in References in this WHO information document.

Other World Wide Web resources - general

Association for the Advancement of Medical Instrumentation (AAMI)
http://www.aami.org
This is a USA website with useful links to information pertaining to the regulation of the medical devices manufacturing industry. Also available to buy from this organization is 'The Quality System Compendium - GMP requirements and Industry Practice' and the accompanying book 'Supplement to the Quality System Compendium'. These books explain in simple language how the clauses from FDA 21 CFR Part 820 can be applied using examples from industry and compare part 820 with the ISO 13485 requirements.

Annex 5: Essential principles relating to devices - simple overview

Essential principles relating to devices are detailed in 'Essential Principles of Safety and Performance of Medical Devices' - GHTF/SG1/N41R9:2005 (or more recent when available). However, as a top-line guide only, the following criteria constitute a simple overview of essential principles relating to devices:

- its use must not compromise health and safety
- design and construction must conform with safety principles
- must be suitable for intended purpose
- must not to be adversely affected by defined transport or storage
- must achieve its intended purpose
- risk versus benefits must be acceptable to user, patient and any other applicable individual
- must have easy-to-use instructions / protocol for use, with reduced risk of error in use and interpretation
- must have acceptable sensitivity, specificity, trueness, repeatability, reproducibility, control of interference and limits of detection
- design must allow for verification by user (positive and negative controls)
- must have traceability of controls and calibrators

Note: Refer to GHTF Final Document (or more recent when available): 'Essential Principles of Safety and Performance of Medical Devices' - GHTF/SG1/N41R9:2005

Annex 6: Model for inspection process

Plan, Do, Check, Act model: