Information for Manufacturers on the Manufacturing Site(s) Inspection
(Assessment of the Quality Management System)

WHO Prequalification of In Vitro Diagnostics Programme
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1. Introduction
The World Health Organization (WHO) Prequalification of In Vitro Diagnostics (IVDs) Programme is coordinated through the department of Essential Medicines and Health Products. The aim of the WHO Prequalification of IVDs Programme is to promote and facilitate access to safe, appropriate and affordable in vitro diagnostics of good quality in an equitable manner. Focus is placed on in vitro diagnostics for priority diseases and their suitability for use in resource-limited settings.

The WHO Prequalification of IVDs Programme undertakes a comprehensive assessment of individual in vitro diagnostics through a standardized procedure aimed at determining if the product meets WHO prequalification requirements. The prequalification assessment process includes three components:
- Review of a product dossier;
- Laboratory evaluation of performance and operational characteristics; and
- Manufacturing site(s) inspection.

Post-market surveillance is a WHO post-qualification activity which includes reactive and proactive measures, through complaint reporting and post-shipment/pre-distribution lot testing. Post-qualification also includes mandatory manufacturer notification of changes to the product or the quality management system.

The findings of the WHO Prequalification of IVDs Programme are used to provide independent technical information on safety, quality and performance of in vitro diagnostics, principally to other United Nations (UN) agencies but also to WHO Member States and other interested organizations. The WHO prequalification status, in conjunction with other procurement criteria, is used by UN agencies, WHO Member States and other interested organizations to guide their procurement of in vitro diagnostics.

2. Intended audience
This document has been prepared to provide manufacturers with information on the assessment of their quality management system for WHO prequalification. In addition, this document is issued to inspection team members.

3. Definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>abbreviated WHO prequalification assessment</td>
<td>Laboratorv evaluation of performance and operational characteristics and abbreviated site inspection.</td>
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1 Prequalification does not imply any approval by WHO of the product and manufacturing site(s). Moreover, prequalification does not constitute any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety, quality, or performance.
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.

dossier review  

Review and assessment of documentation including data, protocols, reports, procedures, etc., to support the quality, safety and performance of an in vitro diagnostic for the purpose of WHO prequalification.

full WHO prequalification assessment  

Review of product dossier, laboratory evaluation of performance and operational characteristics and site inspection.

in vitro diagnostic  

A medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.

WHO laboratory evaluation  

Laboratory-based evaluation of the performance and operational characteristics of a product for the purpose of WHO prequalification.

manufacturer  

Any natural or legal person with responsibility for design and/or manufacture of a diagnostic product with the intention of making the diagnostic product available for use, under his/her name; whether or not such a diagnostic product is designed and/or manufactured by that person himself/herself or on his/her behalf by another person(s).

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 - a 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.

regulatory version - Relates to the information associated with a submission for approval by a regulatory authority. The submitted version is defined by all of the documentation related to development, manufacture, and intended use, labelling and post market surveillance of the product and all the documented evidence supporting the safety and performance claims associated with that submission. If any aspect of this documentation is different in any way between the submissions to different regulatory authorities or assessment bodies (US FDA, Health Canada, a Notified Body for CE marking, etc.) it is considered to be a different regulatory version.

manufacturing site inspection - Inspection of the manufacturing site(s) of product undergoing WHO prequalification.

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.

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

4. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>GHTF</td>
<td>Global Harmonization Task Force</td>
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<td>IMDRF</td>
<td>International Medical Device Regulators Forum</td>
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<td>IVD</td>
<td>in vitro diagnostic</td>
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<td>MDSAP</td>
<td>Medical Device Single Audit Program</td>
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<td>QMS</td>
<td>Quality Management System</td>
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5. Scope

This document describes the application of internationally recognized standards to the prequalification inspection, including the quality management system assessment, and the process facilitated by WHO inspectors together with qualified 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 International Medical Device Regulators Forum (IMDRF). Publications from these organizations are prepared by recognized experts and are referred to by several mature regulatory agencies throughout the world.

The inspection process is based on the referenced standards and guidelines (see Annex 1). Although it is not mandatory for manufacturers to use these standards and guidelines, a quality system and manufacturing process that fulfills 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 criteria for WHO Prequalification of IVDs 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 good practice for the manufacture of IVDs, including other ISO standards, will be utilized during the prequalification assessment. The inspections are based on the principles outlined in ISO 19011:2011 'Guidelines for quality and/or environmental management systems auditing'.

IMPORTANT NOTE: It must be understood that the inspection will not necessarily be limited to aspects described in this document. The inspection will be conducted to reflect the particular IVD(s) and good 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.

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2 formerly Global Harmonization Task Force (GHTF).
6. **The Inspection Process**

6.1. **Objectives and scope of the inspection**

6.1.1. **Objectives of the inspection**

The overall intent of the prequalification inspection is to ensure the supply of quality IVD(s). Therefore, the specific objectives of this process are to ensure compliance of the manufacturer's quality management system and manufacturing practices with international standards, to:

- determine the effectiveness of the implemented quality management system in meeting appropriate quality standards;
- to verify the data supporting the claims presented in the submitted pre-submission form and product dossier; and
- to inspect the quality management system according to the manufacturer's own requirements.

6.1.2. **Scope of the inspection**

The scope of the inspection is limited to the manufacturing site and product(s) agreed upon with the manufacturer. The inspection is product-specific, and more than one product may be assessed in a single inspection. The inspection will include all organizational units, activities and processes associated with these products.

WHO will first assess the documents related to the quality management system to establish the readiness of the Quality Management System (QMS) for inspection (stage 1) and to determine the scope and objectives of the onsite inspection. Such documents may include standard operating procedures and quality records and shall be submitted to WHO, as requested, prior to the inspection.

On-site inspections are performed in a sample audit format. That is, not all details of the manufacturing processes will be examined. However, the expertise of the inspectors will guide them in selecting those processes that are indicative of producing an IVD of good quality.

The inspection will be limited to the time allocated by the inspection team and agreed upon with the manufacturer prior to the inspection. A follow up inspection may be necessary, depending on the criticality and number of identified nonconformities.

**IMPORTANT NOTE:** At the time of the inspection the site of manufacture must be in active production of at least one of the products undergoing prequalification assessment for the inspection team to perform an adequate inspection. In addition, key personnel must be present at the time of the inspection.

6.2. **Principles relating to the inspection**

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

- *Independence*
The inspectors that include WHO staff and selected regulatory and technical experts 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 inspection plan provided to the manufacturer and agreed upon with the manufacturer prior to the inspection. Modification of the plan may occur, to accommodate the manufacturing site’s processes and to follow audit trails 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. The Medical Device Single Audit Program (MDSAP)\(^3\) documents will be used to calculate the time allocated to a particular inspection.

- **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. Representatives of the national regulatory authorities, procurement agencies and other WHO employees may accompany the inspection team to the manufacturing site(s) as observers or for training purposes.

- **Consistency of procedures**
  The inspection procedure shall be performed according to defined guidelines and with a lead inspector to ensure consistency during the inspection. The WHO officer responsible for inspections shall ensure consistency between inspections of the same type and scope.

- **Adequacy of inspection documentation**
  Documentation associated with each inspection, such as inspection reports, shall provide adequate information related to the prequalification assessment of the product and to the post-prequalification phase, 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 shall 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**

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\(^3\) Refer to the document MDSAP AU P0008: Audit Time Calculation Procedure
Inspections are conducted in compliance with the prescribed WHO Prequalification Team quality management system.

6.3. **Types of inspections**

The inspection cycle consists of three types of inspection, which are outlined in this section.

6.3.1. **Initial inspection**

The initial inspection will be performed in two steps:

1) The stage 1 inspection, usually a desk audit, will evaluate the documentation related to the quality management system to ensure readiness for a stage 2 inspection. General information about the documented quality management system, including the quality manual and manufacturing processes, organogram, workflows, critical suppliers and floor plan will be reviewed in the stage 1 inspection to establish the readiness of the QMS and to prepare for an on-site visit. Any issues of concern will be communicated to the manufacturer. A satisfactory stage 1 inspection is a pre-condition for proceeding to the stage 2 inspection.

2) The stage 2 inspection will comprehensively evaluate the effective implementation of the quality management system and implemented production processes through a site(s) inspection. A preliminary report detailing issues of concern (if any) will be provided on the final day of the inspection. A final inspection report including the classified nonconformities will be issued after the inspection.

6.3.2. **Re-Inspection**

Re-inspection may occur when required to ensure ongoing compliance with prequalification requirements. This will either be a partial or full inspection depending on, for example, the type of product, results of inspections by other agencies, feedback from the market such as recalls or complaints, changes to the quality management system or the product(s) since the last inspection. Re-inspections shall typically occur every three to five years after prequalification unless an earlier re-inspection is deemed necessary.

6.3.3. **Special inspection**

This may be required when, for example,

- the effective implementation of corrective actions to address nonconformities has to be verified in a follow up inspection, prior to prequalification;
- substantial changes are made to the IVD’s design, composition, safety and/or performance;
- serious concerns have been raised about the ongoing quality of the IVD;
- production has been suspended and then recommenced; and/or
- there is a significant change in the quality management system.

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4 Refer to the document PQDx_121 WHO procedure for changes to a WHO prequalified in vitro diagnostic
6.3.4. **Abbreviated inspection**

The eligibility for the abbreviated inspection\(^5\) will be established based on the documentation provided with the pre-submission form.

The manufacturer will not have to submit the full quality management system documentation for a stage 1 desktop review. The manufacturer will be requested to submit an information package (refer to Table 4 in the document PQDx_173 “Abbreviated Prequalification Assessment”), that will assist WHO in preparing for the manufacturing site(s) inspection. The onsite inspection time will be calculated and limited to those product and user specific processes, that are a major focus of WHO prequalification inspections (e.g. risk management, in-use stability under poorly controlled conditions, impact on stability of transportation, information gathered from the market etc., user training and material). The inspection will not repeat all activities usually undertaken, but instead rely on the findings of the most recent regulatory audit report. There will be a limited sampling of some of the general quality management processes and a follow up on, or clarification of individual findings identified in the previous report.

6.3.5. **Waiver of site visit.**

A site visit may be waived under defined circumstances such as recent inspection by a WHO recognized regulatory authority or by a Medical Devices Single Audit Program (MDSAP) participating organisation with appropriate scope, the full report and other requested documentation being made available to WHO inspection staff for review. This documentation shall contain sufficient detail on the processes and records related to the type of products in prequalification.

6.4. **Roles and responsibilities**

The lead inspector 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. WHO may delegate such role to an external consultant when deemed appropriate.

6.4.1. **Responsibilities of the lead inspector**

Responsibilities of the lead inspector are in addition to those of an inspector, described below and include:

- plan and prepare the inspection
- communicate with the manufacturer
- assist with the selection of the inspection team members
- define the scope of the inspection
- prepare the inspection plan, working documents, briefing documents and supervise the travel arrangements for the inspectors
- represent the inspection team with the manufacturer
- supervise inspectors during the inspection

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\(^5\) Refer to the document PQDx_171 Abbreviated Prequalification assessment
• 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
• compile the final inspection report (usually within one month), after consultation with the other inspectors, for review and approval by WHO Prequalification Team - Inspection Group Lead
• submit the report to the manufacturer
• follow up on nonconformities.

6.4.2. **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 IVDs requirements for inspections including information in this document
• 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 lead inspector and maintain a means of obtaining prompt guidance during the inspection if required
• bring to the attention of the Lead inspector 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 lead inspector in preparing the report of the inspection
• assist the manufacturers to understand the WHO prequalification requirements

**NOTE:** All notes and other documented evidence gathered at the inspection will be considered confidential part of the WHO records of the inspection
6.4.3. Responsibilities of the manufacturer

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

- agree upon the objectives 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 closing meeting and the receipt of the completed inspection report, and if nonconformities are identified, the manufacturer's responsibilities will be to:

- determine the root cause of all nonconformities identified
- determine the corrections and corrective actions to be taken to address the nonconformities and to appropriately address directly related and / or related systemic issues
- submit a corrective action plan within 30 days after receipt of the final inspection report
- implement and verify the effectiveness of the corrective actions in a timely manner
- inform WHO of the completion of these actions as required
- inform WHO of any subsequent significant change to the quality system or the product.

6.5. Inspection team selection

6.5.1. Composition of the inspection team.

The inspection team may consist of:

- the lead inspector
- a technical inspector who is knowledgeable and experienced in assessing the relevant IVD product. This includes the product realisation processes 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 lead inspector or by a suitably qualified technical auditor)
• an inspector expert in quality control activities including the on-site laboratory, responsible for activities such as final product release (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.
• qualified interpreters who facilitates the communication between the inspection team and the manufacturer’s personnel to support an open and effective communication throughout the inspection.

NOTES: inspectors may fulfill multiple roles. If more than one product or production line is to be inspected, an additional inspector may be added to the team, to reduce the actual time spent on site to a maximum of four days;

The manufacturer will be informed of the identity of the proposed inspection team members 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 prior to 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.

6.5.2. Standard of conduct
All members of the inspection team, all observers and interpreters 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'.

6.6. Dossier review briefing note
As part of the WHO Prequalification of IVDs Programme, the pre-submission form and product dossier shall be submitted to WHO in accordance with specified requirements. A briefing note or dossier review summary report will be prepared by the WHO Prequalification Team - Diagnostics Assessment group and discussed with the lead inspector. The lead inspector will share this information with the quality and technical inspectors in preparation of the onsite inspection. Other documentation reviewed may include previous inspection reports, the quality management documentation review report and the instruction for use of the product(s) in prequalification. Issues arising from these reports will be noted. Any other relevant documentation or information will be made available to all of the participating inspectors for review.
6.7. Logistics, documentation and travel for inspection

6.7.1. 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 lead inspector 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 undergoing prequalification assessment is active (if several products are inspected during the same inspection, the production line for at least one of them must be active);
- quality control activities are being performed; and
- 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 details of the type of audit to be conducted and the sites and products to be inspected, using information from the submitted information on the product and the quality management system, 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
- 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 to the inspection will be calculated according to the MDSAP model⁶, but may vary according to the complexity of the scope of the inspection depending on the number of manufacturing technologies and the number and type of IVDs in prequalification. A sample of an inspection plan is provided in Annex 3. Inspectors will be allocated tasks by the lead inspector according to their expertise and the requirements of the inspection.

6.7.2. Documentation regarding subcontractors, outsourced processes and significant suppliers (critical suppliers)

The manufacturer should have the necessary documentation available to demonstrate that the processes to control such supply are effective. This may include but is not limited to providers of critical raw material, interim components, packaging services or else used to make the IVD, meet relevant quality expectations. The manufacturer shall be responsible for the sufficient control of any critical supplier including outsourced processes. If this requirement is not sufficiently met, a nonconformity against the respective ISO 13485:2003 requirement will be issued and an inspection of subcontractor sites may become necessary.

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⁶ Refer to MDSAP AU P0008: Audit Time Calculation Procedure
6.7.3. Working documents for on-site inspection

Inspectors will be provided with briefing notes as applicable to their area of inspection. The briefing notes may contain information about open questions and/or issues with the product dossier assessment, technical information about the product batches provided for laboratory evaluation or the FIND/WHO rounds of malaria RDTs product testing and do not necessarily define the entire scope of the inspection. Additional items may be included according to the particular requirements of the IVD and the expertise of the inspector.

It is expected that inspectors will document in writing their findings in the inspection notes as the inspection progresses. This information will be used to compile the draft onsite report and to describe any nonconformities and shall be handed over to the lead inspector to gather all relevant inspection records and to compile the final report.

6.7.4. Language for the on-site inspection

The inspection will be conducted in English. To enable a smooth and effective inspection, the relevant higher level quality management documents shall be available in English. Translation needs will be discussed with the manufacturer.

6.7.5. Travel and accommodation arrangements

The lead inspector has the responsibility for 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 safe travel and accommodation arrangements.

7. The Inspection Onsite

7.1. Opening meeting

The opening meeting (1 hour total) is held to exchange information between the inspection team and the manufacturing team on the inspection process and manufacturing site and to confirm the inspection scope, objectives and plan as well as the availability of responsible contact persons onsite. The times indicated below may act as a guide.

7.1.1. Inspection team (20 minutes)

The lead inspector will first:

- Introduce the inspection team;
- review scope and objectives of inspection;
- provide a short summary of the inspection process as part of the prequalification program and confirm the timetable;
- establish official communications links between the manufacturer and the inspection team;
• confirm that the resources and facilities needed by the inspection team are available; and
• allow manufacturer to ask clarifying questions regarding the process.

7.1.2. **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 the quality management system
• provide brief overview of onsite manufacturing process particularly for the product/s to be prequalified
• inform the inspection team of any changes since the submission of the dossier for prequalification and/or the submission of the batches for the WHO laboratory evaluation
• provide a manufacturing schedule including shifts (if applicable) for the inspection days and a diagram for the manufacturing workflow, and
• present samples of the products in prequalification (final product) for the inspection team to investigate content and labelling thereof.

7.2. **The inspection**

7.2.1. **General**

The inspection will seek to confirm the adequacy and effectiveness of the QMS including the technical / production processes and that they represent state of the art practice and include the effective implementation of the manufacturer's documented procedures.

Documents and records from all levels of the quality system will be reviewed. Post-market surveillance data as well as marketing and training material may be included in the review.

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

Evidence will be collected onsite, as follows:
• by examination of documents including standard operating procedures and records
• by visual observation of activities
• by visual observation of environmental conditions
• confirmation of statement of fact that is acquired through interviews
• may include random sampling of product for laboratory testing, and
• may include photographs.

Nonconformities identified during the document review or interviews will be notified to the accompanying representative and may be verified by acquiring additional information where 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 final inspection report.

7.2.2. 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 clause (section) 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 product and system related standards and references may be used by the manufacturer to ensure good practice in the manufacture of the IVDs.

The QMS inspection process includes but is not limited to:

- management (clauses 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 (clauses 4 and 7) including design and development: inspection of these sections is to ensure that the manufacturer has established 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 (clauses 4, 6, 7 and 8): inspection of these sections is to ensure that the manufacturer has established 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 (clauses 8.2.2, 8.5): 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 (7.4): this section is especially important when significant components are outsourced. The manufacturer must ensure that raw material, intermediates, components and services provided by suppliers are of an appropriate standard. Refer 2.7.2 above
- documentation and records (4.2): inspection of this section is to ensure that relevant documents and records are defined, established and 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 (7.2): customers in this context include purchasers and users of the product and relevant regulatory bodies
- training of personnel (6.2): inspection of this section is to ensure that adequate qualifications and training of personnel appropriate to the tasks required of them; training records, and
- adequate infrastructure and work environment (6.3; 6.4): inspection of this section is to ensure the adequacy of facilities, manufacturing, equipment, monitoring and quality control equipment; calibration and maintenance.
7.2.3. Verification of data supporting the product dossier submission

During the inspection, one of the inspectors will sample the quality records and reports that support the data submitted with the product dossier for prequalification. This may include, but is not limited to data recorded for the batches submitted for WHO laboratory evaluation or testing, data collected in performance studies (internal and independent external), quality control data and batch manufacturing records. The manufacturer should ensure that the entire product dossier submitted to WHO is available on site.

7.3. 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 lead inspector will present a brief summary of the day's activities and 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 onsite draft report: the inspectors will then assist the lead inspector in summarizing the outcome of the inspection.

7.4. Daily wrap-up meeting

The manufacturer will be invited to discuss the outcome of every inspection day and any issues of concern (potential nonconformities) as part of the daily wrap up meetings between the manufacturer and the WHO inspection team during the inspection performed on-site. Comments on issues of concern and the performance of the inspection enable the manufacturer to indicate their understanding on any issue of concern, to contest part or all of the issues of concern, or to provide additional clarification on the extent or significance of the issue of concern. If the manufacturer contests the nonconformity, a rationale must be provided including supporting evidence.

7.5. Closing meeting

7.5.1. Summary and draft on-site inspection report

The closing meeting concludes the inspection and will be held in the presence of the complete inspection team and the management team of the manufacturer. Other staff members may be invited by the management, as appropriate.

The outcome of the inspection including areas covered and not covered, limitations to the inspection or the product will be presented. The lead inspector will summarise the findings and issues of concern in the order of significance and present the list of nonconformities or an onsite draft inspection report depending on the type of inspection. The report will describe the main
findings, issues of concern and summarize the general outcome of the inspection. It will contain an annex with substantial, specific information on the nonconforming processes or areas observed by the inspectors and may include an indication of their relative severity (list of nonconformities). The issues of concern will be listed in the order of their severity with those of highest concern on top of the list. The inspectors will be available to provide additional explanation if required.

The manufacturer's management team will have the opportunity to comment on and to seek clarification on items in the draft onsite report from the inspection team. When the manufacturer contests any issue of concern, a rationale must be provided including supporting evidence.

The draft report will allow the manufacturer to start working on any immediately required corrections. A time frame for the implementation of corrective actions should be agreed to if possible at the closing meeting. The final inspection report will clearly indicate that the corrective action plan has to be submitted within 30 days after receipt.

It is intended that an authorized inspection report will be issued by WHO within 30 days of the onsite visit. If an inspection report cannot be issued within this time, the manufacturer will be notified regarding the cause of the delay.

8. Inspection Report

8.1. Overview
The purpose of the 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 IVD
- provide information to the manufacturer on which to base improvements to the quality of the manufacturing system
- provide a permanent record of the findings of the inspection, and
- provide the WHO team with a recommendation of actions following 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 19011:2011 'Guidelines for quality and/or environmental management systems auditing'.

The lead inspector will prepare the document and is responsible for its accuracy and content. A draft report will be left on site on the final day of the inspection. A final report will be available generally within 30 days of the inspection although this time may be extended to two months during periods of high workload and vacation.

Inspection reports will be broadly of two types, as detailed below.
8.1.1. **Reports with no requirements**

The inspection report will be a consensus report compiled by the lead inspector. The participating inspectors may be asked to review the report for accuracy. Following approval by the WHO authorized approver, the report shall be submitted to the manufacturer.

8.1.2. **Reports with requirements (relating to nonconformities)**

The inspection report will be a consensus report compiled by the lead inspector. Following authorization by the WHO authorized approver, the report shall be submitted to the manufacturer. It will include a description of the nonconformities found during the inspection, their severity, the findings that contributed to this nonconformity and the relevant internal quality management document or specific ISO 13485 requirement (individual clause or subclause).

Nonconformities:
During the onsite inspection, nonconformities may have been identified with respect to:
   a) quality management system inspection criteria
   b) verification of data supporting the product dossier claims.

Both types a) and b) nonconformities, as well as the objective evidence contributing to the nonconformity, will be individually stated and described including the inspection criterion that was not met. Additional findings to the same requirement may contribute to the severity grading of a nonconformity, thus raising its level.

The severity of nonconformities will be classified according to the GHTF SG3 N19:2012 document. Accordingly, level 1 to level 5 nonconformities can be assigned with level 1 being the lowest level and level 5 the most critical level of nonconformity.

The quality management system shall be considered deficient, should the following findings occur:
- One (1) or more level 5 nonconformity(s)
  or
- Seven (7) or more level 4 nonconformities.

In this case, the manufacturer will be invited to submit a corrective action plan to be reviewed and commented by WHO; If the manufacturer will not be able to properly address the above nonconformities within an agreed time period, the application will be closed due to severity and number of the nonconformities. A new application for prequalification will not be accepted before sufficient evidence demonstrating that the nonconformities have been properly addressed will be submitted.

A corrective action plan (CAP) shall be submitted by the manufacturer within 30 days after receipt of the final inspection report. For each identified nonconformity, the CAP shall include:
- root cause analysis,
- correction,
- corrective action,
- timeline,
- responsibilities, and
- evaluation of the effective implementation of the corrective action(s).

Although the manufacturer’s format for CAPs will be sufficient, the manufacturer should provide the CAP to WHO in an editable format such as Excel spreadsheet. This enables improved communication on the approval / disapproval or request for additional information and documents by the lead inspector.

The lead inspector will ask for and will review submissions from the manufacturer relating to correction of the nonconformities. The lead inspector 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 lead inspector 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 lead inspector will request an improved CAP and may ask for further evidence that must be presented within 30 days after the first review report on CAP was sent to the manufacturer
- before finalizing the inspection, all nonconformities must have been appropriately addressed by the manufacturer
- if the effective implementation of corrective actions cannot be evaluated by document review, a follow up inspection must be conducted within six (6) months of the initial inspection
- if more than six months elapse before the manufacturer provides satisfactory responses, the application will be closed and a new application required.

8.2. Contents of the inspection report

The main components of the inspection report shall include:

- purpose, scope and objectives of the inspection including the site(s), processes and the product(s)
- details of the WHO inspection team
- details of the areas covered in the inspection
- limitation of the inspection or product
- 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 will include 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’.
8.3. Retention of inspection reports
Retention of reports and associated documentation shall be for the period of 3 consecutive inspections and for 5 years following the last inspection.

8.4. Review of corrective action plans to remedy nonconformities
The lead inspector will be responsible for requesting, reviewing and reporting on the manufacturer's responses to nonconformities observed during the inspection.

The manufacturer will have a maximum of two opportunities to supply the necessary information to address nonconformities in a timely manner, usually within 30 days of the request. However, the nature of some nonconformities 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 application for WHO Prequalification will be terminated.

8.5. 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. The lead inspector also notifies the WHO authorized person that the inspection and follow-up are complete.

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.

8.6. 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 (deficient quality system)
- falsification of data or submitted evidence or deliberate misrepresentation of facts regarding the manufacturing and quality system (level 5 nonconformity)
- excessive number of nonconformities identified (see above)
- 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, and/or
- failure of the manufacturer to respond adequately to requests for submissions relating to nonconformities.

8.7. WHO internal review of the inspection process
An internal review of the inspection documents and the process is carried out to ensure high quality of the inspection process.

The internal review ensures consistency of the work relating to inspections within the WHO prequalification team.
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.

References

International Organization for Standardization (ISO):

- ISO 13485:2003 Medical devices - Quality management systems - Requirements for regulatory purposes
- ISO 19011:2011 Guidelines for quality and/or environmental management systems auditing.
- ISO 14971:2007 Medical devices - Application of risk management to medical devices
  Note: EN ISO 14971:2012 applies only to manufacturers placing devices on the market in Europe; for the rest of the world, ISO 14971:2007 remains the applicable standard.
- ISO 9000:2005 Quality management systems - Fundamentals and vocabulary
- ISO 15223-1:2012 Symbols to be used with medical device labels, labelling and information supplied—Part 1 General requirements

Global Harmonization Task Force (GHTF), now available on the IMDRF site:

- GHTF.SG4 (99)28 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(pd1)/N33R16:2007 Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers - Part 3: Regulatory Audit Reports
- GHTF/SG1/N70:2011 Label and Instructions for Use for Medical Devices
- GHTF/SG5/N8:2012 Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices
- GHTF/SG3/N15R8 Implementation of risk management principles and activities within a Quality Management System.
• GHTF/SG3/N15R6:2013 Risk management as an integral part of the quality management system in draft (Date of information - 26 July 13).
  Note on 26 July 13: Risk management as an integral part of the quality management system in draft (SG3/N15R6)

WHO
• Overview of the Prequalification of IVDs assessment process (PQDx_007)
• Abbreviated Prequalification assessment (PQDx_171)

WHO and CLSI

IMDRF MDSAP (Medical Device Single Audit Program) documents as used in the piloting programme:
• MDSAP AU P0008: Audit Time Calculation Procedure
• MDSAP_AU_F0008.1_Audit_Time_Calculation_Spreadsheet
• MDSAP_AU_P0019_QMS_Audit_Reports_Policy

Other Reference Documents (European Commission):
The standards listed at the following website are harmonized standards and thus lead to presumption of conformity with the relevant essential requirements of Directive 98/79/EC:

Annex 2: Example of inspection time table

The table below is an example of a time table for a WHO 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.

<table>
<thead>
<tr>
<th>Time</th>
<th>Inspection Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td><strong>9.00 - 10.00</strong> Opening meeting</td>
</tr>
<tr>
<td></td>
<td>Introduction of personnel and overview of inspection by WHO lead inspector; overview of manufacturing process, principle staff and quality system from manufacturer.</td>
</tr>
<tr>
<td></td>
<td><strong>10.00-11.30</strong> Facility tour</td>
</tr>
<tr>
<td></td>
<td><strong>11.30- - 13.00</strong> Inspection (includes 15 minute break)</td>
</tr>
<tr>
<td></td>
<td>Quality System: Management responsibility (5) including interviewing of senior management.</td>
</tr>
<tr>
<td></td>
<td>Planning of product realization (7.1), Customer-related processes (7.2), Design and development (7.3), Purchasing (7.4)</td>
</tr>
<tr>
<td></td>
<td>Quality System: Quality management system (4).</td>
</tr>
<tr>
<td></td>
<td>Production and service provision (7.5), Control of monitoring and measuring devices (7.6)</td>
</tr>
<tr>
<td></td>
<td><strong>13.00-13.45</strong> Lunch break (onsite)</td>
</tr>
<tr>
<td></td>
<td><strong>13.45 - 17.00</strong> Inspection (continued)</td>
</tr>
<tr>
<td></td>
<td>Quality System: Resource management (6), Measurement Analysis &amp; improvement (8)</td>
</tr>
<tr>
<td></td>
<td><strong>16.45-17.00</strong> Daily wrap up meeting: Inspectors report briefly to manufacturers on day's findings</td>
</tr>
<tr>
<td>Days 2-3</td>
<td>All day</td>
</tr>
<tr>
<td></td>
<td>Short opening meeting to schedule activities</td>
</tr>
<tr>
<td></td>
<td>Inspection continued as above and as required including breaks</td>
</tr>
<tr>
<td></td>
<td>Daily wrap up meeting</td>
</tr>
<tr>
<td>Final day</td>
<td><strong>9.00 - 12.30</strong> Inspection (continued)</td>
</tr>
<tr>
<td></td>
<td><strong>12.30 - 13.15</strong> Lunch break (onsite)</td>
</tr>
<tr>
<td></td>
<td><strong>13.15 - 16.00</strong> Inspectors meeting: discuss findings, prepare draft onsite report</td>
</tr>
<tr>
<td></td>
<td><strong>16.00 - 17.00</strong> Closing meeting: present inspection outcome and draft report and discuss findings with manufacturer</td>
</tr>
</tbody>
</table>
Annex 3: 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*

International Medical Device Regulators Forum (former: Global Harmonization Task Force (GHTF) documents are now located in the IMDRF “Documents” folder)
www.imdrf.org (former 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, as well as 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 IMDRF / 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/jgs/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) – here for Switzerland, see national website as appropriate
http://www.iso.ch
Follow link 11. 'Health care technology'

Link to full list of medical device standards and technical reports
The two important standards pertaining to the manufacture of medical devices (that includes medical diagnostic test kits) are 13485:2003 and TR 14969:2004 (Technical Report). 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 4: Essential principles relating to IVDs - simple overview

Essential principles relating to IVDs 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 IVDs:

- its use must not compromise health and safety
- design and construction must conform with safety principles
- must be suitable for intended purpose
- must not 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 meet acceptable performance specifications such as 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

Further explanation and guidance on preparing a checklist to demonstrate conformity with the essential principles can be found in 'Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of IVD Medical Devices (STED)' Study Group 1 Proposed Document SG1(PD)/N063.