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

WHO Prequalification of In Vitro Diagnostics
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1. Introduction

The World Health Organization (WHO) Prequalification of In Vitro Diagnostics (IVDs) is coordinated through the department of Essential Medicines and Health Products. Focus is placed on in vitro diagnostics for priority diseases and their suitability for use in resource-limited settings.

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

The full prequalification assessment process includes the following components:

- review of a product dossier;
- performance evaluation including operational characteristics;
- inspection of manufacturing site(s); and
- labelling review.

The abridged prequalification assessment includes the following components:

- performance evaluation including operational characteristics;
- abridged inspection of manufacturing site(s); and
- labelling review.

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

- prequalification commitments;
- annual reporting;
- reporting of changes;
- post-market surveillance obligations;
- re-inspection; and
- on-going compliance with WHO prequalification technical specifications.

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

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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.
2. **Intended audience**

This document has been prepared to provide manufacturers with information on the inspection of manufacturing site(s) of product(s) undergoing WHO prequalification assessment, including the assessment of their quality management system. In addition, this document is issued to inspection team members.

3. **Definitions**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>abridged WHO prequalification assessment</td>
<td>Prequalification assessment including performance evaluation, abridged inspection of manufacturing site(s) and labelling review.</td>
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<td>inspection of manufacturing site(s) or “inspection”</td>
<td>On-site inspection of the manufacturing site(s) of product undergoing WHO prequalification of IVDs assessment</td>
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<td>inspector</td>
<td>A person with relevant qualifications and competence to perform inspections or specified parts of such inspections and who belongs to, or is authorized by, the World Health Organization</td>
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<td>dossier review</td>
<td>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.</td>
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<tr>
<td>full WHO prequalification assessment</td>
<td>Prequalification assessment including dossier review, performance evaluation, inspection of manufacturing site(s) and labelling review</td>
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<td>in vitro diagnostic medical device (IVD)</td>
<td>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</td>
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<td>Note: IVDs include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles, and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.</td>
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<tr>
<td>performance evaluation</td>
<td>Performance evaluation including evaluation of operational characteristics of a product for the purpose of the prequalification assessment process.</td>
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<tr>
<td>manufacturer</td>
<td>Any natural or legal person with responsibility for design and/or...</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>manufacture of a diagnostic</td>
<td>The non-fulfilment of specified requirements within the planned arrangements.</td>
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<tr>
<td>product</td>
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<tr>
<td>nonconformity or noncompliance</td>
<td>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.</td>
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<td>nonconformance</td>
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<td>objective evidence</td>
<td>Statement of fact made during a quality inspection and substantiated by objective evidence.</td>
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<tr>
<td>observation</td>
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<td>Quality Management System or QMS</td>
<td>Set of interrelated or interacting elements of an organization to establish quality policies and quality objectives and to establish the processes that are needed to ensure that those policies are followed and those objectives are achieved. [ISO 9000:2015].</td>
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<td>regulatory version</td>
<td>Relates to the information associated with a submission for approval by a regulatory authority. The submitted version is defined by all of the documentation related to development, manufacture, and intended use, labelling and post market surveillance of the product and all the documented evidence supporting the safety and performance claims associated with that submission. If any aspect of this documentation 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.</td>
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<td>subcontractor</td>
<td>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.</td>
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4. Abbreviations

<table>
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<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>ISO</td>
<td>International Organization for Standardization</td>
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<td>IVD</td>
<td>in vitro diagnostic medical device</td>
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<tr>
<td>MDSAP</td>
<td>Medical Device Single Audit Program</td>
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<tr>
<td>QMS</td>
<td>Quality Management System</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>UN</td>
<td>United Nations</td>
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5. Scope

This document describes the application of internationally recognized standards and guidelines to the inspection of manufacturing site(s), including the quality management system assessment. 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 process for an inspection of a manufacturing site is based on the standards, guidelines and other reference documents listed in Annex 1. 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 must indicate which standards are used to establish and maintain the quality management system and the manufacturing process under which the product to be prequalified is manufactured.

The inspection of manufacturing site(s) is based on the principles outlined in ISO 19011:2011 Guidelines for auditing management systems. Additional references relating to good practice for the manufacture of IVDs, including other ISO standards, will be utilized during the prequalification assessment.

As a general overview, the criteria for inspection of manufacturing site(s) 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.

In March 2016, the International Organization for Standardization (ISO) published a new revision to ISO 13485, which replaces the previous version from 2003. Until 1 March 2019, ISO 13485:2003 and ISO 13485:2016 will coexist, allowing for users of ISO 13485 to transition to the 2016 revision of the standard. It is recommended that the users of ISO 13485:2003 work with their certification body to schedule an upgrade inspection within the transition period.

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2 formerly Global Harmonization Task Force (GHTF).
An inspection of a manufacturing site based on ISO13485:2003 will continue to be conducted by the WHO until 1 January 2019 (aligning closely with the end of the ISO transition period on 1 March 2019), unless, prior to the commencement of the manufacturing site inspection, the manufacturer communicates to WHO its preference to use the newer standard (ISO13485:2016 or EN ISO13485:2016).

**IMPORTANT NOTE:** The manufacturing site inspection will not necessarily be limited to aspects described in this document. The manufacturing site inspection will be conducted taking into account 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 and read in conjunction with the reference documents listed in Annexes. More detailed explanation of the topics in this document can be found in these reference documents.

### 6. The Process for the Inspection of a Manufacturing Site(s)

#### 6.1. Objectives and scope of the inspection of manufacturing site(s)

**6.1.1. Objectives of the inspection of manufacturing site(s)**

The overall intent of the manufacturing site inspection is to assess the safety, performance and quality of commercially available IVD(s). Therefore, the specific objectives of this process are to assess 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;
- verify the data supporting the claims presented in the submitted pre-submission form and product dossier; and
- inspect the quality management system according to the manufacturer's own requirements.

**6.1.2. Scope of the inspection of manufacturing site(s)**

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

The initial manufacturing site inspection will be performed in two stages. In the Stage 1 inspection, usually in the form of a desk audit, WHO will first assess the documents related to the quality management system and establish the readiness for the Stage 2 on-site inspection, and to determine the scope and objectives of the on-site inspection. Such documents may include, without limitation, standard operating procedures and quality records. The manufacturer must submit to WHO, as requested, all of the aforementioned documents prior to the commencement of the inspection of the manufacturing site.
On-site inspections are a sampling process. That is, not all details of the manufacturer’s quality management system 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 of the manufacturing site will be limited to the time allocated by the inspection team and agreed upon with the manufacturer prior to the inspection.

**IMPORTANT NOTE:** At the time of the inspection of the manufacturing site, the manufacturing site must be in active production of at least one, or part, of the products undergoing prequalification assessment in order for the inspection of the manufacturing site to proceed and to enable the inspection team to perform an adequate inspection. In addition, key personnel must be present at the time of the inspection of the manufacturing site, and the inspection team must have access to all areas and documentation relevant to the production of the aforementioned products.

### 6.2. Principles relating to the inspection of manufacturing site(s)

The following are considered guiding principles governing the inspection of manufacturing site(s):

- **Independence**
  The inspectors that include WHO staff members and selected regulatory and technical experts shall be impartial and free from influences that could affect their objectivity.

- **Inspection objectives and scope**
  The objectives and scope of the inspection of the manufacturing site 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 be with a view to obtain inspection results that are highly reliable.

- **Competence of the inspection team**
  The inspection team shall consist of WHO staff and external experts appointed by WHO (inspectors) with inspection 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 of WHO Member States, representatives of other United Nations agencies, and other WHO staff members 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 enable consistency during the inspection. The WHO staff member responsible for inspections will oversee 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 confidential information and documentation related to the inspection, and shall comply with the applicable WHO standards of conduct and WHO conflict of interest rules. Within these considerations, the inspection process is to be transparent to all participants.

• **Inspection results and conclusions**
  The results and conclusions of the inspection 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. The grading of nonconformities is the responsibility of WHO, including the final release of all reports.

• **Quality system**
  Inspections are conducted in compliance with the prescribed WHO Prequalification Team quality management system.

### 6.3. Types of inspections

The programme of inspections of a manufacturing site consists of four types of inspections, which are outlined in this section.

#### 6.3.1. Initial inspection

The initial inspection will be performed in two stages:

1) The Stage 1 inspection, usually a desk audit, will evaluate the documentation related to the quality management system to establish 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 an on-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 of the manufacturing site may occur when required by WHO to ensure ongoing compliance with prequalification requirements. This will either be a partial (also known as a surveillance inspection) or full inspection depending on, for example, the type of product, results of inspections by WHO-recognized national regulatory authority, feedback from the market such as recalls or complaints, and/or changes to the quality management system, manufacturing site or the product(s) since the last inspection. Routine re-inspections shall typically occur every three to five
years after prequalification of the product by WHO, unless an earlier re-inspection is deemed necessary by WHO.

### 6.3.3. Special inspection

A special inspection may be required when, for example,

- the effective implementation of corrective actions to prevent the recurrence of nonconformities needs 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 \(^3\);
- 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.

### 6.3.4. Inspection for an Abridged Prequalification Assessment

The eligibility for the inspection with an abridged scope \(^4\) will be established by WHO based on the documentation provided with the pre-submission form.

If the product qualifies for an inspection with an abridged scope, the manufacturer will not have to submit the full quality management system documentation for a Stage 1 inspection. The manufacturer however must submit upon request by WHO an information package (refer to Table 4: Information Package Contents in the document PQDx_173 “Abridged Prequalification Assessment”), that will assist WHO in preparing for the manufacturing site(s) inspection. The on-site inspection time will be limited and calculated for selected product(s) and key processes for that site (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). An inspection with an abridged scope will not necessarily include a review of all QMS procedures and processes that are usually inspected, as it will take into consideration the findings of the most recent regulatory audit reports (full and surveillance). There will be a limited sampling of some of the general quality management processes and a follow up, or clarification of, individual findings identified in the previous report.

### 6.3.5. Waiver of manufacturing site inspection.

An inspection of a manufacturing site(s) may be waived by WHO in writing under defined circumstances such as; a recent inspection with appropriate scope by a WHO-recognized national regulatory authority or by a Medical Devices Single Audit Program (MDSAP) participating Auditing Organisation. The full report and other requested documentation must be made available to WHO inspection staff members for review. This documentation shall contain sufficient detail on the processes and records related to the type of products in prequalification. WHO will take into account any objective evidence contained within an MDSAP audit report that demonstrates compliance with medical device prequalification requirements.

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\(^3\) Refer to the document PQDx_121 WHO procedure for changes to a WHO prequalified in vitro diagnostic

\(^4\) Refer to the document PQDx_173 Abridged Prequalification assessment
6.4. Roles and responsibilities of the inspectors and manufacturers for an inspection

The lead inspector, who is generally a WHO staff member, has responsibility for all phases of the inspection and has authority to make final decisions regarding the conduct of, and observations made, during the inspection. WHO may delegate such role to an external expert appointed by WHO, when deemed appropriate by WHO.

Where the lead inspector is not a WHO staff member, all communications with the manufacturer will be the responsibility of the WHO co-inspector participating in the inspection. Further, the WHO co-inspector is responsible for compiling the final report and submitting it for internal WHO review in a timely manner.

The manufacturer is required to nominate a point of contact for the Inspection team who will ensure that the responsibilities of the manufacturer for the inspection are met.

6.4.1. Responsibilities of the inspectors and lead inspector who are staff members of WHO

Responsibilities of the WHO lead inspector are, to:

- 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 and/or review the inspection plan, working documents, and briefing documents if prepared by a co-inspector
- supervise the travel arrangements for the inspectors
- represent the inspection team with the manufacturer
- supervise inspectors during the inspection
- communicate any obstacles regarding the inspection to the manufacturer and to WHO prior to or during the inspection
- prepare and present the general outcome of the inspection of the manufacturing site, 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
- submit the report to the manufacturer
- follow up on nonconformities.
- assist the manufacturers to understand the WHO prequalification requirements

When the lead inspector is not a WHO staff member, some of these responsibilities will be delegated to a member of the inspection team who is a WHO employee.

6.4.2. Responsibilities of all inspectors involved in the inspection

The responsibilities of each inspector, including the lead inspector, who are not staff members of WHO are to:

- use established inspection methods to achieve consistency in the inspection process
• plan and carry out assigned responsibilities objectively, effectively and efficiently within the scope of the inspection of the manufacturing site
• safeguard confidentiality of confidential documents and information in association with the inspection
• comply with the WHO standard of conduct and conflict of interest rules
• comply with the WHO 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 and/or WHO inspector(s), in a timely manner, any indications or observations that could influence the results of 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 and/or WHO inspector(s) in preparing the inspection report

NOTE: All notes and other documented evidence gathered in connection with the inspection will be considered confidential and 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. Among other things, the manufacturer's responsibilities will be to:
• agree upon the objectives and the scope of the inspection with the WHO prequalification team
• inform the WHO prequalification team of any issues that may affect an effective and efficient inspection process
• cooperate with the inspectors to ensure that the objectives of the inspection are achieved
• identify a person responsible for coordinating and facilitating, on behalf of the manufacturer, the inspection process
• inform relevant employees and personnel about the objectives and the scope of the inspection
• appoint responsible members of staff to accompany members of the inspection team
• ensure inspectors are aware of health, safety and other applicable requirements
• provide on-site resources, such as a meeting room, for the inspection team in order to ensure an effective and efficient inspection process
• provide full 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.

If nonconformities are identified at the inspection of the manufacturing site these will be discussed with, and provided to, the manufacturer during the closing meeting. The manufacturer will subsequently receive an inspection report that will include the nonconformities. Upon receipt of the inspection report the manufacturer's responsibilities will be to:
• determine the root cause of all nonconformities identified
• determine the corrections for the nonconformities, and the corrective actions to be taken to prevent recurrence of the nonconformities
• submit a corrective action plan to WHO 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 corrective 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 for manufacturing site.

The inspection team may consist of:
• the lead inspector
• one or more technical inspector(s) who are knowledgeable and experienced in assessing the relevant IVD product, including the product realisation processes and resultant product.
• a quality management systems inspector who is qualified and experienced to inspect the quality management system of the type of manufacturer being inspected (this role may be performed by the WHO inspector or by a suitably qualified technical inspector)
• an inspector who is an 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 interpreter(s) who facilitate(s) the communication between the inspection team and the manufacturer’s personnel to support an open and effective communication throughout the inspection.

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

Before undertaking work relating to the inspection, each external inspector, assessor or technical expert will be required to complete and sign the WHO declaration of interests form. If, based on the above-mentioned declaration of interests, WHO considers that there is no risk of a real or perceived conflict of interest (or WHO considers that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the assessor or inspector in question to undertake the work relating to the inspection, then he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

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

6.5.3. Standard of conduct

All members of the inspection team, as well as 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, the pre-submission form and product dossier shall be submitted by the manufacturer 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 WHO inspector. The WHO inspector will share this information with the quality and technical inspectors in preparation of the on-site 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 of the manufacturing site

6.7.1. Dates and time allocated for the inspection of manufacturing site(s)

The dates and time allocated for the inspection are to be agreed upon by all participants under the guidance of the WHO 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 inspection 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 scope and purpose of the inspection of the manufacturing site
- identification of inspection team members
- date and place of the 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 complexity of the scope of the inspection, the number of manufacturing technologies, and the number and type of IVDs in prequalification. An example of an inspection timetable is provided in Annex 2 to this document. Inspectors will be allocated tasks by the WHO 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 must have the necessary documentation available to demonstrate that the processes to control product supply are effective and meet the relevant quality expectations. This includes, but is not limited to, documentation relating to providers of critical raw material, interim components, packaging services or other used to make the IVD. 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 requirement will be issued and an inspection of subcontractor sites may be necessary.

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 performance evaluation, 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 on-site report and to describe any nonconformities and shall be handed over to the WHO inspector to gather all relevant inspection records and to compile the final inspection 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 manufacturer must ensure that all 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 WHO inspector has the responsibility for organization of the travel and accommodation arrangements for the inspection team. This responsibility will not extend to the observers, except under particular circumstances, such as when WHO is providing training or education. If requested by WHO the manufacturer will use its local knowledge to assist with safe travel and accommodation arrangements for the inspection team.

7. The On-site Inspection

7.1. Opening meeting

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

7.1.1. Inspection team

The lead inspector will first:
- Introduce the inspection team;
- review scope and objectives of the inspection;
- provide a short summary of the inspection process as part of the WHO prequalification of IVDs assessment;
- confirm the timetable of the manufacturing site inspection;
- confirm that the resources and facilities needed by the inspection team are available; and
- allow manufacturer to ask clarifying questions regarding the inspection process.

7.1.2. Manufacturer

Then, the manufacturer will:
- introduce its principal staff
- provide a current organigram and a written list with contact details of its staff, to facilitate access to key personnel during the inspection process
- provide brief overview of the quality management system
- provide brief overview of on-site manufacturing process, particularly for the product/s to be prequalified
inform the inspection team of any changes since the submission of the product dossier or last inspection for prequalification and/or the submission of the batches for the WHO performance 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 of a manufacturing site

7.2.1. General

The inspection will seek to confirm the adequacy and effectiveness of the manufacturer’s documented QMS, with emphasis on the control of the production processes and compliance with state of the art practices, including WHO technical guidelines.

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 on-site, as follows:

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

Nonconformities identified during the document review or interviews will be notified to the accompanying representative of the manufacturer 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. Note that ISO13485 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 the following processes:

- management: inspection of management processes is to ensure that an adequate and effective quality management system is in place, including management review
• product documentation, 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: 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: 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: 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 to section 6.7.2 above
• documentation and records: 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: customers in this context include purchasers and users of the product and relevant regulatory bodies
• training of personnel: 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: 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 WHO prequalification. This may include, but is not limited to, data recorded for the batches submitted for WHO performance evaluation or testing, data collected in performance studies (internal and independent external), quality control data and batch manufacturing records. The manufacturer must 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. The following meetings should, at minimum, take place
• Discussion of findings and the progress of the inspection.
• Daily summary, a brief summary of the day's activities and findings.
• Inspection summary: On the last day of the inspection, the inspectors will meet to discuss and summarize the findings to be left with the manufacturer
7.4. Daily wrap-up meeting
Daily wrap-up meetings will be held between the manufacturer and the inspection team at the end of each day of the on-site inspection. As part of these daily wrap-up meetings, the inspection team will present a summary of the daily findings and the manufacturer will be invited to discuss the findings and any issues of concern (potential nonconformities).

During the daily wrap-up meetings, the manufacturer must raise any comments on any issues of concern or the performance of the inspection, indicate its understanding of, or contest, any issues of concern raised, and/or provide additional clarification to the inspection team on the extent or significance of any issue of concern. If the manufacturer contests any nonconformity or issue of concern, a rationale (including supporting evidence) must be provided by the manufacturer to the inspection team.

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 lead inspector will summarise the findings and issues of concern from the inspection, in the order of significance, and will present: (i) the outcome of the inspection, including areas covered and not covered as well as limitations to the inspection or the product; and (ii) the list of nonconformities or a draft onsite inspection report, depending on the type of inspection. If draft onsite inspection report is presented, the report will describe the main findings and issues of concern, and will summarize the general outcome of the inspection. Significant issues of concern will be discussed in detail with the manufacturer. The inspectors will be available to provide additional clarifications concerning the inspection, if requested by the manufacturer.

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

The list of nonconformities or a draft onsite inspection report will allow the manufacturer to start working on any immediately required corrections. A time frame for the issuing of the Final Inspection Report and the implementation of corrective actions should be agreed to at the closing meeting, if possible. The lead inspector will advise the manufacturer that the corrective action plan has to be submitted within 30 days from the receipt of the Final Inspection Report.
8. Report for a Manufacturing Site Inspection

8.1. Overview
The purpose of the inspection report is to:

- provide the manufacturer with information on nonconformities found at the inspection. To be eligible for WHO prequalification of the IVD product inspected, the identified examples of nonconformity must be corrected by the manufacturer and investigated to determine correction actions that are intended to prevent recurrence of the nonconformity.
- provide information to the manufacturer upon 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 of the inspection report is found in guidance such as IMDRF/MDSAP WG/N24 FINAL: 2015 – Medical Device Regulatory Audit Reports and ISO 19011:2011 Guidelines for auditing management systems.

The WHO inspector will prepare the inspection report and is responsible for its accuracy and content. A final inspection report will be issued by WHO to the manufacturer generally within 30 days of the inspection, although this time may be extended to two months during periods of high workload and vacation. If a final inspection report cannot be issued within such 30-day timeframe, the manufacturer will be notified regarding the delay.

The manufacturer understands and agrees that WHO will have absolute, exclusive, unfettered control over the manner in which the inspection is carried out, including the publication of the results of the inspection, regardless of the outcome. The manufacturer also understands and agrees that WHO reserves the right to share the manufacturer’s prequalification application and related information, as well as the results of the inspection and the full inspection reports, including any drafts thereof and including (subject to appropriate obligations of confidentiality) any confidential information to which WHO may gain access in the course of the prequalification process and/or inspection, with the relevant authorities of any interested Member State of the Organization, with interested National Regulatory Authorities (NRAs), and with relevant inter-governmental organizations. As used herein, “Confidential information” means: (i) confidential intellectual property, know-how and trade secrets (including, e.g., formulas, processes or information contained or embodied in a product, unpublished aspects of trade mark, patents, etc.); and (ii) commercial confidences (e.g., structures and development plans of a company).

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

The inspection report with no requirements 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 with requirements relating to nonconformities will be a consensus report compiled by the lead inspector. Following authorization by the WHO-authorized approver, the report will be submitted to the manufacturer. This type of report will include a description of the nonconformities found during the manufacturing site inspection, their severity, the findings that contributed to each nonconformity, the relevant specific ISO 13485 requirements (individual clause or subclause) and the evidence of nonconformity (e.g. manufacturer’s procedure)

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

Both types of nonconformities, as well as the objective evidence contributing to the nonconformity, including the inspection criterion that was not met, will be individually stated and described in the manufacturing site inspection report. 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 critically deficient, if the following findings occur:
   - One (1) or more level 5 nonconformity(s); or
   - Seven (7) or more level 4 nonconformities.

If any nonconformities are included in the final inspection report, a corrective action plan (CAP) shall be submitted to WHO by the manufacturer within 30 days after receipt of the final inspection report. For each identified nonconformity, the CAP shall include:
   - a root cause analysis,
   - the corrections required for the identified nonconformities,
   - the corrective actions required to remove the cause and to prevent recurrence,
   - a timeline for implementation of corrections and corrective actions,
   - the resources responsible for implementation, and
   - evaluation of the effective implementation of the corrective action(s).

The manufacturer must provide the CAP to WHO in an editable format such as Word document or Excel spreadsheet. This enables improved communication on the approval, rejection, or for a request for additional information and documents by WHO.
The WHO inspector will request, and the inspection team will review submissions from the manufacturer relating to correction of the nonconformities. Thereafter, one of the following outcomes may occur, as applicable:

- if the submissions are acceptable to WHO, the WHO inspector will notify the manufacturer by letter that the inspection and follow-up are complete;
- if the manufacturer’s corrective action plan (CAP) submissions are not acceptable to WHO, the WHO inspector will request an improved CAP and may ask the manufacturer for further evidence.
  - In such cases, both the improved CAP and the additional evidence must be presented by the manufacturer to WHO within 30 days after the first review report on CAP is sent to the manufacturer;
- if the effective implementation of corrective actions cannot be evaluated by document review, a follow-up inspection will be required before the nonconformities may be closed out.

Before finalizing the manufacturing site inspection, all nonconformities identified in the inspection report must have been satisfactorily corrected (as determined by WHO) by the manufacturer.

However if a satisfactory outcome is not reached, for example, if;

- the manufacturer does not submit (whether timely or at all) a corrective action plan to WHO; or
- the manufacturer is unable to implement all agreed corrections and corrective actions during the agreed time period; or
- more than six months have elapsed after the initial inspection and the manufacturer has still not provided WHO with satisfactory responses to the identified nonconformities, then the manufacturer’s application for WHO prequalification of the product(s) inspected will be terminated by WHO and a new application will be required.

Any subsequent application for WHO prequalification will not be accepted unless and until the manufacturer submits sufficient evidence demonstrating that the nonconformities have been properly corrected. If the manufacturer’s QMS is found critically deficient, a re-inspection and review of any available additional data will take place before the inspection component may be completed.

8.2. Notice of Concern (NOC):
A notice of concern (NOC) is a letter that is issued by WHO to a manufacturer to remind such manufacturer of its obligation to maintain quality assurance procedures and practices, as well as to inform suppliers and procurement agencies of any potential risks associated with a given product or manufacturer.

An NOC states observations made during an inspection that are considered to be:
• “critical” or “major” non-compliances with WHO norms, requirements and standards, that are of concern in relation to quality management or quality assurance; or
• “critical” or “major” non-compliances with WHO norms, requirements and standards, that were not satisfactorily addressed in the response from the manufacturer to an inspection.

An NOC is not necessarily a cause for public concern. However, if WHO does identify a public health risk linked to a given product or manufacturer, then WHO will take appropriate additional steps, including provision of advice to the public. These steps may include:

- suspension of products included on the WHO List of Prequalified IVDs;
- issuing of a compulsory variation to temporarily or permanently suspend the use of a manufacturing site;
- recall of batches of products on the WHO List of Prequalified IVDs that have been supplied by a manufacturer; and/or
- rejection of applications for prequalification assessment submitted by the manufacturer.

An NOC may be issued by WHO to a manufacturer, if:

- observations were made during an inspection that indicate poor compliance or failure to comply with the applicable WHO norms, standards or requirements;
- the response to the observations noted in an inspection report, detailing the corrective actions taken or proposed to be taken, is considered by the lead inspector to be insufficiently robust and unlikely to deal with the underlying root cause of a critical or major nonconformity; this may include not providing suitable objective evidence of corrective actions;
- the requested response to the observations noted in an inspection report, detailing the corrective actions taken or proposed to be taken, was not received by WHO on or before the due date (i.e. 30 days from the inspection date);
- if a manufacturer refuses inspection of a manufacturing site.

If immediate public health concerns have been identified during the inspection, or if the inspection observations relate to misrepresentation of data, falsification or manipulation of data with the intent to deceive, the NOC will be posted immediately on WHO’s website. WHO has a zero tolerance policy in relation to such activities since they indicate a serious quality system failure that should be urgently addressed by the senior management of the manufacturer.

An NOC will remain on the WHO’s website until adequate and appropriate corrective actions have been implemented effectively by the manufacturer concerned and verified by WHO.

8.3. NOC appeal rights

An NOC contains the factual observations made during an inspection. These will have been discussed during the inspection and listed in the inspection report. Generally, the facts that form the basis of the observations are not in dispute. However, the manufacturer may disagree that a risk exists, or with the level of risk identified by WHO, that has resulted in the issuing of the NOC.
If the manufacturer disagrees with any aspect of the inspection report and subsequent NOC, they should send information by email to WHO that gives the basis for the disagreement. (pregualinspection@who.int, indicating Coordinator, WHO in the subject line). The matter will then be investigated and a response provided within 15 days. Should the manufacturer not be satisfied with the response, the manufacturer should email;

Head, Regulation of Health products and Technologies (RHT)
RHTinfo@who.int
Attention: Head, RHT in the subject line.

All feedback will be treated in confidence and without prejudice.

8.4. Contents of the report for the inspection of a manufacturing site(s)

The main components of the inspection report shall include:

- purpose, scope and objectives of the inspection, including the manufacturing site(s), processes and the product(s)
- details of the 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'.

8.5. Retention of inspection reports

WHO and the manufacturer shall retain inspection reports and associated documentation for the period of 3 consecutive inspections and for 5 years following the last inspection.

8.6. Review of corrective action plans to remedy nonconformities

The WHO 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 WHO with the necessary information to correct nonconformities and implement corrective actions to prevent recurrence in a timely manner. The manufacturer will supply such information and correct the nonconformities identified during the inspection within 30 days of the request for information, unless WHO agrees in writing (given the nature of the nonconformities) to grant the manufacturer an extended time period to supply the requested information. Consideration may be given to justifiable requests for an extension of time to respond.
In certain cases, WHO may agree, in its sole discretion, to permit the manufacturer to correct specific nonconformities after prequalification, provided that the manufacturer commits in writing to correct them by an agreed deadline. Such a “commitment to prequalification” will be reflected in the WHO prequalification public report and will be verified during the re-inspection. Failure to comply with prequalification commitments within agreed deadlines will result in the delisting from the WHO list of prequalified IVDs.

8.7. Completion of the inspection of a manufacturing site(s)

When the identified nonconformities have been corrected, corrective actions to prevent recurrence have been implemented by the manufacturer as requested by WHO, and the results accepted by WHO, the manufacturer will receive a letter advising them of the completion of the inspection process.

The re-inspection period will be determined by WHO using a risk management approach after all of the information from the product dossier review, performance evaluation and inspection are collated.

8.8. 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 not be recommended for inclusion in WHO’s List of Prequalified In Vitro Diagnostics Products. Criteria/reasons used for not recommending a product’s inclusion may include: (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 level 4 identified (see 8.1.2)
- 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.

8.9. WHO internal review of the inspection process for a manufacturing site(s)

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

The internal review assesses consistency of the work relating to manufacturing site inspections within the WHO prequalification team.
Annexes

Annex 1: Reference documents

Note: Standards and other reference documents are constantly being updated. The manufacturer must directly refer to the third party sources listed below in order to obtain the most up-to-date versions of the following standards and other reference documents.

References

International Organization for Standardization (ISO):

- ISO 13485:2003 and 2016 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 (This standard has been revised by ISO 13485:2016)
- 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 9000:2015 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/SG1/N071:2012 - Definition of the Terms `Medical Device` and In Vitro Diagnostic (IVD) Medical Device`
- GHTF/SG1/N70:2011 - Label and Instructions for Use for Medical Devices
- GHTF/SG3/N18:2010 - Quality management system - Medical Devices - Guidance on corrective action and preventive action and related QMS processes
- GHTF/SG3/N15R8 - Implementation of risk management principles and activities within a Quality Management System.
WHO
- Overview of the Prequalification of IVDs assessment process (PQDx_007)
- Abridged Prequalification assessment (PQDx_173)

WHO and CLSI

IMDRF MDSAP (Medical Device Single Audit Program) documents as used in the piloting programme:
- MDSAP AU P0008: Audit Time Determination Procedure
- MDSAP_AU_F0008.1:AuditDuration Calculation form
- MDSAP_AU_P0019: Medical Device Regulatory 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:

### Annex 2: Example of inspection time table for a manufacturing site(s)

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 on-site inspection will vary according to inspection requirements.

<table>
<thead>
<tr>
<th>Time</th>
<th>Inspection Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td><strong>9.00 - 10.00</strong> Opening meeting \nIntroduction of personnel and overview of the manufacturing site inspection by WHO lead inspector; overview of manufacturing process, principle staff and quality system from manufacturer.</td>
</tr>
<tr>
<td>10.00-11.30</td>
<td>Facility tour</td>
</tr>
<tr>
<td>11.30-13.00</td>
<td>Inspection of one or more of the following processes: \nQuality System: Management responsibility including interviewing of senior management. \nPlanning of product realization, Customer-related processes, Design and development, Purchasing \nQuality System: Quality management system. \nProduction and service provision, Control of monitoring and measuring devices \nQuality System: Resource management, Measurement Analysis &amp; improvement</td>
</tr>
<tr>
<td>13.00-13.45</td>
<td>Lunch break (onsite)</td>
</tr>
<tr>
<td>13.45 – 16.45</td>
<td>Inspection (continued) \nOne or more of the above QMS processes</td>
</tr>
<tr>
<td>16.45-17.00</td>
<td>Daily wrap up meeting: Inspectors report briefly to manufacturers on day's findings</td>
</tr>
<tr>
<td><strong>Days 2-3</strong></td>
<td>All day \nShort opening meeting to schedule activities \nInspection continued as above and as required including breaks \nDaily wrap up meeting</td>
</tr>
<tr>
<td><strong>Final day</strong></td>
<td>9.00 - 12.30 Inspection (continued)</td>
</tr>
<tr>
<td>12.30 - 13.15</td>
<td>Lunch break (onsite)</td>
</tr>
<tr>
<td>13.15 - 16.00</td>
<td>Inspectors meeting: discuss findings, prepare draft onsite report</td>
</tr>
<tr>
<td>16.00 - 17.00</td>
<td>Closing meeting: present outcome and draft report of the inspection of the manufacturing site(s), and discuss findings with manufacturer</td>
</tr>
</tbody>
</table>
Annex 3: Internet resources

The resources listed below are available on the internet. This list of Internet Resources is provided to assist manufacturers in preparation for a manufacturing site inspection. This list is not intended to be exhaustive and manufacturers can access any sources that will assist them in preparation for an 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 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/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) – 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 ISO13485 and ISO TR 14969 (Technical Report). These can be purchased 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 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 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.