WHO PREQUALIFICATION TEAM:
DIAGNOSTICS

World Health Organization

The Assessment Process for Listing of WHO Prequalification Evaluating Laboratories for IVDs

Information for Candidate Laboratories

WHO Prequalification of In Vitro Diagnostics

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1 Abbreviations and definitions

1.1 Abbreviations

CAP	Corrective action plan
EOI	Expression of interest
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
IVD	in vitro diagnostic
QMS	Quality management system
WHO	World Health Organization

1.2 Definitions

Audit: systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled. [reference 1 definition 3.9.1]

Auditor: person with the demonstrated personal attributes and competence to conduct an audit [reference 1 definition 3.9.9]

Audit findings: results of the evaluation of the collected audit evidence against audit criteria
NOTE: Audit findings can indicate either conformity or nonconformity with audit criteria or opportunities for improvement. [reference 1 definition 3.9.5]

Audit plan: description of the activities and arrangements for an audit**.** [reference 1 definition 3.9.12]

Audit scope: extent and boundaries of an audit
NOTE: The audit scope generally includes a description of the physical locations, organizational units, activities and processes, as well as the time period covered. [reference 1 definition 3.9.14]

Audit team: one or more auditors conducting an audit, supported if needed by technical experts**.** [reference 1 definition 3.9.10]

Competence: demonstrated personal attributes and demonstrated ability to apply knowledge and skills. demonstrated ability to apply knowledge and skills [reference 1 definition 3.1.6]

Corrective Action: action to eliminate the cause of a detected nonconformity or other undesirable situation [reference 1 definition 3.6.5]

Evidence: records, statements of fact or other information, which are relevant to the audit criteria and verifiable. [reference 1 definition 3.9.4]

Nonconformity: non-fulfilment of a requirement. [reference 1 definition 3.6.2]

Performance evaluation: investigation of a device intended to become an IVD medical device for the purpose of establishing or verifying its performance claims. [reference 2 definition 3.52]

Quality management system: management system to direct and control an organization with regard to quality. [reference 1 definition 3.2.3]

Technical expert: person who provides specific knowledge or expertise to the audit team **.** [reference 1 definition 3.9.11]

WHO Prequalification Evaluating Laboratories for In Vitro Diagnostics: Laboratories listed by WHO to undertake performance evaluations of in vitro diagnostics undergoing WHO prequalification assessment.

2 Scope

This document describes the World Health Organization (WHO) process to assess the suitability of candidate laboratories having submitted an Expression of Interest (EOI) to conduct performance evaluations of in vitro diagnostics (IVDs) for WHO prequalification purposes.

3 Introduction

The WHO Prequalification Programme is coordinated through the Department of Essential Medicines and Health Products. The aim of the programme is to promote and facilitate access to safe, appropriate and affordable IVDs of good quality in an equitable manner. Focus is placed on IVDs for priority diseases and their suitability for use in resource-limited settings.

The WHO Prequalification Programme undertakes a comprehensive assessment of individual IVDs 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;
- Performance evaluation by a WHO Prequalification Evaluating Laboratory; and
- Manufacturing site(s) inspection.

In May 2016, WHO invited laboratories with potential to undertake performance evaluations for WHO prequalification submit an EOI. A formal mechanism to assess the suitability of these laboratories has been developed. Successful laboratories will be listed as WHO Prequalification Evaluating Laboratories.

The process of assessment of the candidate laboratories by WHO consists of the following:

- Receipt of an EOI;
- Stage 1 audit- Assessment of EOI and specific quality management system (QMS) documentation;
- Stage 2 audit- On-site audit of the laboratory to assess compliance with WHO requirements; and
- Listing of successful laboratories as WHO Prequalification Evaluating Laboratories.

WHO requirements for candidate laboratories are based on the principles laid out in international standards and guidelines [3] referenced in this document and other aspects relevant to prequalification. The various stages of the assessment verify compliance with these requirements. Further information on WHO prequalification can be found at the following link.

4 The assessment process

WHO requirements for listing of Prequalification Evaluating Laboratories are specifically related to performance evaluations. The assessment will ascertain the potential for laboratories to undertake a performance evaluation according to the relevant WHO protocol, as well as the laboratory's compliance with the principles of ISO/IEC 17025:2005 [4] and ISO 15189:2012 [5, 6]. Additional references relating to good practice for laboratories performing IVD evaluations, including other ISO standards, will be utilized during the audit. The auditing process is based on the principles outlined in ISO 19011:2011 [7]. The assessment process will follow the guiding principles set out in Annex 1.

5 Stage 1 Audit: Review of QMS documentation

For the Stage 1 audit, WHO will assess the EOI submission to establish the potential compliance of the laboratory to WHO requirements. Such documents will include attachments specified in the EOI submission form.

The Stage 1 audit is a desk top audit. During this audit, general information about the documented QMS, including the quality manual, relevant standard operating procedures for the specific validated methodology(ies), relevant validation reports and proficiency testing evaluation reports of the specific method(s), organogram, and floor plan will be assessed. Specific records may also be requested by letter to evaluate effective implementation of specific laboratory procedures. The laboratory will be given one opportunity to provide extra documentation, if needed. Documentation must be received in the time period specified for the assessment process to proceed.

A report describing the outcome of the Stage 1 audit will be communicated to the laboratory. A satisfactory Stage 1 audit is a pre-condition for proceeding to a Stage 2 audit. Applications from unsuccessful candidate laboratories will not undergo any further assessment.

6 Stage 2 Audit: On-site audit of the laboratory

The Stage 2 audit is the on-site audit to ensure implementation of an effective QMS and to confirm the ability of the laboratory to conduct performance evaluations of specific types of IVD(s). The specific objectives are to:

- verify the information supporting the claims presented in the EOI submission and other Stage 1 audit documentation; and
- determine the effectiveness of the implemented QMS in meeting appropriate quality standards and laboratories own requirements.

All organizational units, activities and processes associated with specified IVD performance evaluations may be audited. Documents and records from all levels of the QMS will be sampled and reviewed. Informal interviews of personnel at all levels and discussions with persons selected by the auditor will form part of the audit process.

6.1 Roles and responsibilities

6.1.1 Responsibilities of WHO

WHO is responsible for the following activities associated with the on-site audit.

- plan and prepare the audit;
- communicate with the laboratory;
- define the scope of the audit;
- prepare the audit plan, working documents, briefing documents and supervise the travel arrangements for the auditors;
- communicate any challenges regarding the audit to the laboratory management prior to or during the audit;
- prepare and present the draft audit report to the laboratory management at the closing meeting on the final day of the audit;
- submit the final report to the laboratory; and
- follow-up on nonconformities with a request for a detailed corrective action plan (CAP) from the laboratory.

These activities will usually be the responsibility of the WHO lead auditor.

6.1.2 Responsibilities of the laboratory

Responsibilities of the laboratory will be communicated to the laboratory prior to the audit. In general, the laboratory's responsibilities will be to:

- agree upon the objectives and the scope of the audit with the WHO team;
- inform WHO of any major changes to the QMS since the document review was performed;
- inform the WHO team of any issues that may affect an effective and efficient audit process;
- cooperate with the auditors to ensure that the audit objectives are achieved;
- identify a person responsible for coordinating and facilitating the audit process;
- inform relevant employees about the objectives and the scope of the audit;
- appoint responsible members of staff to accompany members of the audit team and to ensure auditors are aware of health, safety and other applicable requirements;
- provide on-site resources, for the audit team, to ensure an effective and efficient audit process, such as meeting rooms;
- provide access to the laboratory facilities, documents and records and other evidence as requested by the auditors in a timely manner to ensure an effective and efficient audit process and so that the audit timetable can be met.

6.1.3 WHO audit team

The audit team will have experience and knowledge in laboratory QMS, performance evaluations and the specific IVDs. Normally a team will consist of two members.

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

All members of the audit team are obliged to act according to the requirements of the WHO International Civil Service Commission "Standards of Conduct for the International Civil Service"[8].

6.2 Logistics for the on-site audit

6.2.1 Dates and time allocated for the audit

The dates and time allocated for the audit are to be agreed upon by all participants.

It is the responsibility of the laboratory to ensure that during the audit the laboratory is performing routine testing and the key personnel for the QMS and laboratory activities are present.

WHO will provide the audit plan at least two weeks before the audit and will include details of the audit to be conducted using information from the submitted documentation on the QMS, 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 audit.

The audit plan will include:

- the audit scope and purpose;
- identification of audit team members; and
- date and place of audit, expected time and duration of each audit activity including meetings to be held with the laboratory's management team.

6.2.2 Language for the on-site audit

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

6.2.3 Travel and accommodation arrangements

WHO is responsible for the travel and accommodation arrangements of the audit team and all associated costs with the audit team. However, the laboratory will generally be asked to provide advice for these arrangements.

6.3 Meetings during the audit

6.3.1 Opening meeting

The opening meeting (approximately 1 hour total) is held to exchange information between the audit team and the laboratory team on the audit process, to confirm the audit scope, objectives and plan as well as the availability of responsible persons on-site.
Audit team (20 minutes approximately)
The lead auditor will:

- introduce the audit team;

- explain the functions and responsibilities of the WHO audit team;
- make sure that the Attendance Register is completed;
- explain the purpose, and objectives of audit;
- provide a short summary of the audit process as part of the WHO Prequalification Programme;
- confirm the audit plan including:
    - the areas/activities of facility to be covered;
    - requirement for access to selected documents, records, reports; and
    - the timetable for the audit (see an example in Annex 2);
- introduce the methods to be used for the auditing, checklists and classification of findings;
- establish official communications links between the laboratory and the audit team;
- confirm that the resources and facilities needed by the audit team are available;
- allow the laboratory personnel to ask clarifying questions regarding the process;
- allow the audit team to seek clarification regarding the laboratory.

Laboratory (40 minutes approximately)
The laboratory will:

- introduce principle staff;
- provide an organogram (with photographs if possible) and a written list with contact details for key personnel during the audit process;
- provide brief overview of the QMS;
- provide brief overview of the laboratory particularly for the testing of the IVDs to be evaluated;
- inform the audit team of any changes since the submission of information about the laboratory to WHO; and
- provide an activity schedule including shifts (if applicable) for the audit days.

6.3.2 Meeting of auditors

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

- Discussion of findings: during the course of the audit, the auditors will confer regularly and informally regarding the progress of the audit.
- Daily summary: At the conclusion of each day (or at the beginning of the following day), the lead auditor will present a brief summary of the day's activities and findings.
- Audit summary: At the conclusion of the audit process on the last day of the audit, the auditors will meet to discuss their findings in detail.
- Preparation of on-site draft audit report: the auditors will then assist the lead auditor in summarizing any nonconformities found at the audit.

6.3.3 Daily wrap-up meeting

The laboratory staff will be invited to discuss the outcomes and any issues of concern (potential nonconformities) at the end of every audit day. This meeting allows the laboratory to discuss/clarify any issues of concern. If the laboratory contests a nonconformity, a rationale must be provided to WHO in writing including supporting evidence.

6.3.4 Closing meeting

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

The outcome of the audit including areas covered and not covered and limitations to the audit will be presented. The audit team will summarise the findings and issues of concern in the order of significance and present the list of nonconformities that will be rated for severity in a format of a draft audit report.

6.4 Issuance of the final report of the on-site audit

The final audit report will be issued by WHO within 60 days of the on-site visit. If an audit report cannot be issued within this time, the laboratory will be notified regarding the cause of the delay.

6.4.1 Content of the Reports

The final report will describe the main findings, issues of concern and summarize the general outcome of the audit. It will contain an annex with substantial, specific information on the nonconformities observed by the auditors.

6.4.2 Reports with no requirements

If no nonconformities were recorded, WHO will notify the laboratory by letter of successful completion of the on–site audit. Notification of the laboratory listing will be provided in a separate letter.

6.4.3 Reports with requirements (relating to nonconformities)

The report will include a description of the nonconformities found during the audit, their severity, findings that contributed to this nonconformity and the relevant internal QMS document or specific requirement in the standard (individual clause or subclause). The severity of nonconformities will be classified into major, minor findings or observations. The laboratory will be expected to take appropriate action to address the nonconformities before listing.

6.5 Laboratory Corrective action plan

A proposed CAP shall be submitted by the laboratory within 10 days after receipt of the final audit report. For each identified nonconformity, the CAP shall include:

- root cause analysis;
- immediate action taken where applicable;
- corrective action;
- timeline to correct the nonconformity; and
- person(s) responsible.

Where evidence exists that an identified nonconformity has been fulfilled, documentary evidence of this should accompany the CAP. The laboratory should provide the CAP to WHO in an editable format such as Excel spreadsheet.

The laboratory will have a maximum of two opportunities to supply the necessary information to address nonconformities in a timely manner, usually within 10 working 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 laboratory fails to respond adequately to requests for submissions relating to nonconformities in the requested timeframe, the application for WHO laboratory listing may be terminated.

6.6 WHO review of corrective action plan

Before finalizing the audit, all nonconformities must have been appropriately addressed by the laboratory.

Following WHO review of the initial CAP and associated documentation, one of the following outcomes may occur:

- if the submissions are acceptable, WHO will notify the laboratory by letter that the audit and follow-up are complete. Notification of the laboratory listing will be provided under a separate letter.
- if the submissions are not acceptable, the lead auditor will request an improved CAP and may ask for further evidence that must be presented within 10 days after the first review report on CAP was sent to the laboratory. The laboratory will have a maximum of two opportunities to submit a CAP.

If the laboratory is unable to properly address the nonconformities, the application will/may be closed according to the severity and number of the nonconformities.

7 Completion of the assessment process for listing

Laboratories meeting assessment requirements will be informed by letter of listing by WHO.

8 Maintaining compliance

WHO Prequalification Evaluating Laboratories must ensure ongoing compliance with WHO requirements following listing. Relevant external quality assessment reports must be submitted to WHO on an annual basis.

8.1 Re-assessment

Re-assessment of the laboratory may occur as required to ensure ongoing compliance with WHO requirements and relevant standards. This will either be a partial or full audit. Mandatory re-assessments shall occur every three to five years after laboratory listing unless an earlier re-audit is deemed necessary.

Annex 1: **Principles relating to the WHO assessment**

Independence
The auditors, that include WHO staff and QMS and technical experts, shall be impartial and free from influences that could affect their objectivity.

Audit objectives and scope
The audit objectives and scope shall be defined in a general audit plan provided to the laboratory and agreed upon with the laboratory prior to the audit. Modification of the plan may occur, to accommodate the laboratory processes and to follow audit trails depending on the observations made at the time of the audit.

Roles and responsibilities
Roles and responsibilities of all personnel involved in the assessment shall be clearly defined so that expectations can be met and accountableness maintained.

Resources
Resources shall be adequate in terms of competent auditors, expertise as deemed necessary, time allocation and access to external technical and other information. The resources utilized shall ensure that the audit results are highly reliable.

Competence of the audit team
The audit team shall consist of auditors with appropriate skills, education and experience in QMS auditing and IVDs.

Consistency of procedures
The audit procedure shall be performed according to defined guidelines (ISO 19011:2011) using a WHO checklist to ensure consistency for all audits.

Confidentiality and standard of conduct
The auditors shall maintain confidentiality with regard to information and documentation related to the audit and the laboratory/organization and shall comply with the defined WHO standards of conduct. Within these considerations, the audit process is to be transparent to all participants.

Audit results and conclusions
The results and conclusions of the audits shall be consistent and accurate subject to the normal limitations of an audit, noting that the objective evidence collected during the audit is generally a sample.

Quality system
Audits are conducted in compliance with the relevant auditing standards

Annex 2: **Example of audit time table**

The table below is an example of a time table for a WHO audit of a laboratory. Times may be modified to better comply with the daily routine. Length of the site visit will vary according to audit requirements.

	Time	Audit Activity –WHO Lead Auditor	Audit Activity –Technical Auditor
Day 1	8.30 – 9.00	Team briefing meeting and audit Preparation with team.	
	9.00 – 10.00	Opening meeting as per Opening meeting agenda. Introduction of personnel and overview of audit by WHO; overview of laboratory processes, principle staff and QMS by the laboratory.	
	10.00 – 11.30	Facility tour	
	11.30 – 13.00	Horizontal Audits (includes 15 minute break) QMS: Management responsibility including interviewing of senior management. • Organization and Management System • Document Control / Record Control • External Services and supplies • Service to the customer and complaints • Control of nonconforming work • Improvement • CAP • Internal Audits • Managements Reviews	Assessment of technical competence. This includes the Observations of performance of tests / vertical audits and interviews. Technical audit includes but is not limited to: • Personnel • Accommodation and environment • Pre-examination (sourcing and handling of panels) • Methods & method validation • Ensuring Quality of examinations • Equipment • Reporting the results
	13.00 – 13.45	Lunch break (on-site)	
	13.45 – 17.00	Audit (continued)	
	16.45 – 17.00	Daily wrap up meeting: Auditors report briefly to laboratory personnel on day's findings	
Days 2-3	All day	Short opening meeting to schedule activities Audit continued as above and as required including breaks Daily wrap up meeting	
Final day	9.00 – 12.30	Audit (continued)	
	12.30 – 13.15	Lunch break (on-site)	
	13.15 – 16.00	Auditors meeting: discuss findings, prepare draft on-site report	
	16.00 – 17.00	Closing meeting: present audit outcome and draft report and discuss findings with laboratory	

9 References

1 ISO 9000:2015 Quality management systems — Fundamentals and vocabulary. Geneva, Switzerland; 2015. International Organization for Standardization.

2 ISO 18113-1:2009. In vitro diagnostic medical IVDs - Information supplied by the manufacturer (labelling) - Part 1: Terms, definitions and general requirements. Geneva, Switzerland; 2009. International Organization for Standardization.

3 Information and documents on laboratory accreditation can be found on the ILAC (International Laboratory Accreditation Cooperation): www.ilac.org - [website] [Accessed 23 May 2016]

4 ISO/IEC 17025:2005 General requirements for the competence of testing and calibration laboratories; Geneva, Switzerland. 2005. International Organization for Standardization/ International Electrotechnical Commission.

5 ISO 15189:2012 Medical laboratories — Particular requirements for quality and competence. Geneva, Switzerland; 2012. International Organization for Standardization.

6 ISO/TR 22869:2005 Medical laboratories — Guidance on laboratory implementation of ISO 15189:2003. Geneva, Switzerland; 2005. International Organization for Standardization.

7 ISO 19011:2011 Guidelines for quality and/or environmental management systems auditing. Geneva, Switzerland; 2011. International Organization for Standardization.

8 WHO International Civil Service Commission “Standards of Conduct for the International Civil Service” [webpage] [Accessed 19 May 2016] http://icsc.un.org/resources/pdfs/general/standardsE.pdf