



# **OVERVIEW OF THE PREQUALIFICATION OF IN VITRO DIAGNOSTICS ASSESSMENT**

## *WHO Prequalification of In Vitro Diagnostics*

NOTE: Additional technical revisions/updates to this document are currently being formulated by WHO and are expected to be published by 31 March 2017

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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 IVDs for priority diseases and their suitability for use in resource-limited settings.

The WHO Prequalification of IVDs undertakes a comprehensive quality assessment of individual IVDs through a standardized procedure aimed at determining if the product meets WHO prequalification requirements. The full prequalification assessment process includes three components:

- Review of a product dossier;
- Laboratory evaluation of performance and operational characteristics; and
- Manufacturing site(s) inspection.

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

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

## 2. Intended audience

This document has been prepared to provide manufacturers with an overview of the process for WHO In Vitro Diagnostics prequalification assessment (the “prequalification assessment process”). It is recommended that manufacturers wishing to apply for WHO prequalification of their product(s) read this document before applying for prequalification, so that manufacturers are aware of and prepared for all stages of the prequalification assessment process.

## 3. Definitions

abbreviated WHO prequalification assessment	Laboratory evaluation of performance and operational characteristics and abbreviated manufacturing site inspection.
dossier review	Review and assessment of documentation including data, protocols, reports, procedures, etc., to support the quality, safety and performance of an in vitro diagnostic for the purpose of WHO prequalification.
full WHO prequalification assessment	Review of product dossier, laboratory evaluation of performance and operational characteristics and manufacturing site inspection.
in vitro diagnostic	A medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide

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<sup>1</sup> 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.

information for diagnostic, monitoring or compatibility purposes.

laboratory evaluation	Laboratory-based evaluation of the performance and operational characteristics of a product for the purpose of WHO prequalification.
manufacturer	Any natural or legal person with responsibility for design and/or manufacture of a diagnostic product with the intention of making the diagnostic product available for use, under his/her name; whether or not such a diagnostic product is designed and/or manufactured by that person himself/herself or on his/her behalf by another person(s).
re-branded product	A product to be one that is manufactured under identical conditions at the same manufacturing site(s) as the original product. In other words, a "re-branded" product is identical in every aspect to the product manufactured by the original manufacturer, except that the product is labeled with the "re-branded" product name and purchaser identifier.
re-brander	A manufacturer of a re-branded in vitro diagnostic.
regulatory version	Relates to the information associated with a submission for approval by a regulatory authority. The submitted version is defined by all of the documentation related to development, manufacture, and intended use, labelling and post market surveillance of the product and all the documented evidence supporting the safety and performance claims associated with that submission. If any aspect of this documentation is different in any way between the submissions to different regulatory authorities or assessment bodies (US FDA, Health Canada, a Notified Body for CE marking, etc.) it is considered to be a different regulatory version.
manufacturing site inspection	Inspection of the manufacturing site(s) of product undergoing WHO prequalification.

#### 4. Abbreviations

GHTF	Global Harmonization Task Force
IMDRF	International Medical Device Regulators Forum
IVD	in vitro diagnostic
OEM	original equipment manufacturer
SOP	WHO standard operating procedure
WHO	World Health Organization
UN	United Nations

#### 5. About prequalification of IVDs and procurement

The goal of the WHO Prequalification of IVDs is assess the safety, quality and performance of commercially available IVDs for the purpose of providing guidance to interested UN agencies and WHO Member States in their procurement decisions.

To ensure that WHO can prequalify IVDs as efficiently as possible, manufacturers must be fully prepared for the prequalification assessment process when they apply for WHO prequalification. Manufacturers may wish to contact the WHO Prequalification Team – Diagnostics Assessment (e-mail: [diagnostics@who.int](mailto:diagnostics@who.int)) to commence discussions regarding prequalification before applying.

Once a product has been prequalified, it is included in the WHO list of prequalified IVDs and becomes eligible to be invited into the procurement processes of UN agencies. WHO Member States are invited to use the WHO list of prequalified IVDs for their respective procurement decisions. UN agencies and WHO Member States using information from the WHO prequalification of IVDs process should nevertheless perform additional steps of qualification prior to purchasing products included in the WHO list of prequalified IVDs, including steps such as ensuring the supplier's financing stability and standing, ability to supply the required quantities of the product, security of the supply chain, preshipment quality control, and other relevant aspects.

## 6. Eligibility for prequalification of IVDs

### 6.1. Original manufacturer

Applications to the WHO Prequalification of IVDs are only accepted from the legal manufacturer of the product.<sup>2</sup>

### 6.1. "Re-branding" arrangements

WHO is aware that several manufacturers purchase finalized and semi-finalized products from other companies, and then "re-brand" and place these products on the market under their own name/brand. Such products are also known as original equipment manufacturer (OEM) products.

WHO considers a "re-branded" product to be one that is manufactured under identical conditions at the same manufacturing site(s) as the original product. In other words, a "re-branded" product is identical in every aspect to the product manufactured by the original manufacturer, except that the product is labeled with the "re-branded" product name and purchaser identifier.

WHO encourages joint applications by original equipment manufacturers and "re-branders". Submissions for "re-branded" or OEM products will be considered based on the prioritization criteria (refer to Section 7.2).

A condition for the prequalification assessment of a "re-branded" product is that the original product manufacturer and the "re-brander" explicitly consent to the public disclosure by WHO of this "re-branding" arrangement. Such disclosure will include the recommendation that the two products should not be used in combination within the same testing algorithm in the WHO prequalification public report.

## 7. Applying for WHO prequalification

### 7.1. Pre-submission form and supportive documentation

The manufacturer should complete the pre-submission form "PQDx\_015 Pre-Submission Form" and provide all supportive documentation as requested in accordance with the WHO document

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<sup>2</sup> The definition for manufacturer is based on the definition used by the GHTF, and later adopted by IMDRF. This internationally accepted approach of defining a manufacturer has been adopted to ensure that there is a clear understanding of the term "manufacturer" across international markets. For further details visit the following website: <http://www.imdrf.org/>

"PQDx\_017 Instructions for the Completion of the Prequalification of In Vitro Diagnostics Pre-submission Form".

The pre-submission form and the respective attachments (authorization letter, instructions for use and abbreviated assessment eligibility annex) must be submitted electronically to WHO for review. A completed pre-submission form provides summary information about the product, its regulatory version and the manufacturer. The information contained within this form will inform WHO in its decision to prioritize (or not) the product submitted for prequalification, to determine if the product is eligible for abbreviated prequalification assessment, and to plan for each of the elements of the prequalification assessment process. It is therefore important the Pre-Submission Form be completed with accuracy.

The version of the instructions for use submitted along with the pre-submission form will be considered the official version submitted for prequalification assessment. During prequalification, manufacturers cannot make changes to this version of the instructions for use without prior written notification to WHO. Any changes to such version must be agreed in writing by WHO prior to their implementation or the application may be terminated.

WHO reviews the pre-submission form to determine the regulatory version intended for prequalification and if the product meets the WHO prequalification prioritization criteria and other programme suitability aspects.

## **7.2. Prioritization for prequalification**

In order to meet the needs of WHO Member States and UN agencies, WHO prioritizes products submitted for prequalification taking into account the following principles:

- Need for IVDs for a particular disease or disease state;
- Appropriateness of the product for use in resource-limited settings;
- Requests from WHO Member States for particular IVDs;
- Performance characteristics of particular IVDs; and/or
- Availability of prequalified products that are of a similar test format and/or test principle.

The prioritization principles are applied using the following WHO Prequalification of IVDs prioritization criteria:<sup>3</sup>

- Products already listed on the WHO procurement scheme and procured by UN organizations in significant levels;
- Products which assist in the diagnosis and/or monitoring of infection with **HIV-1/HIV-2**, the diagnosis and/or monitoring of infection with **hepatitis C**, and diagnosis of infection with **malaria** parasites;
- Products in a rapid test format and/or technologies that can be used at or near to point-of-care (POC);
- Products that are manufactured by original product manufacturers;
- Product categories for which there exists few other prequalified products<sup>4</sup>.

The prioritization criteria are periodically reviewed in consultation with other UN agencies, WHO programmes and technical experts and are made publicly available by WHO.

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<sup>3</sup> WHO reserves the right to prioritize diagnostics according to other criteria dependent on changing global health needs, the particular needs of WHO Member States, and the emergence of new and relevant diagnostic technologies.

<sup>4</sup> This document only applies to in vitro diagnostics. Male circumcision devices' assessment is defined in a separate document.

The pre-submission form and supportive documentation will be reviewed against the above WHO Prequalification of IVDs prioritization criteria. The manufacturer may receive a communication requesting clarification to assist the prioritization decision.

If the product meets the WHO prequalification prioritization criteria, a non-refundable first fee will be levied. WHO will then determine the type of prequalification assessment, which can either be full or abbreviated (see Section 8 and 9). Upon payment of the first fee, the manufacturer will be notified if the product will undergo full assessment and therefore will receive an invitation to submit a product dossier. Alternatively, the manufacturer will be notified that the product will undergo the abbreviated assessment whereby a product dossier submission to WHO is not required.

### **7.3. Product dossier submission and screening**

For a full prequalification assessment, WHO will formally invite the manufacturer to submit a product dossier. The manufacturer should compile and submit the product dossier as prescribed by WHO documents "PQDx\_018 Instructions for Compilation of a Product Dossier" and "PQDx\_049 Product Dossier Checklist". Manufacturers should not submit a product dossier or pay fees unless instructed to do so by WHO. Product dossiers that are submitted without a request from WHO will be destroyed without review.

Information that was previously submitted in the pre-submission form will be considered by WHO during the review of the product dossier. Therefore, manufacturers should ensure that the content of the product dossier is consistent with the information submitted in the pre-submission form and that any changes in the information submitted in or as part of the pre-submission form are promptly notified in writing to WHO. The product dossier must only include information in support of the product name, product code(s), regulatory version and manufacturing site(s) prioritized by WHO.

Once the product dossier has been received by WHO, it will be screened for completeness by WHO staff before being evaluated. This screening does not take into consideration the technical appropriateness of all the information provided within the product dossier. If the product dossier is incomplete, the manufacturer will be informed that an incomplete dossier has been received and will be requested to provide supplemental information to complete the dossier within a specified time period. There will be two opportunities for the manufacturer to submit the required supplemental information within the timelines set by WHO. In the event of non-compliance, the product dossier will be rejected on grounds of incompleteness and the application will be terminated pursuant to Section 10.3. Dossiers that are considered complete as a result of the screening will be retained by WHO for prequalification assessment.

If the product dossier is determined to be complete and is accepted for prequalification assessment, the manufacturer will be informed of this by letter from WHO. The manufacturer must complete, sign and return to WHO this letter, which will serve as an agreement between WHO and the manufacturer for the participation of the product in the prequalification assessment process, and as a commitment by the manufacturer to comply with the provisions of the prequalification assessment procedures.

## 8. Full prequalification assessment

The full prequalification assessment process consists of three components (refer Figure 1):

- Review of the product dossier;
- Laboratory evaluation of performance and operational characteristics; and
- Manufacturing site(s) inspection.

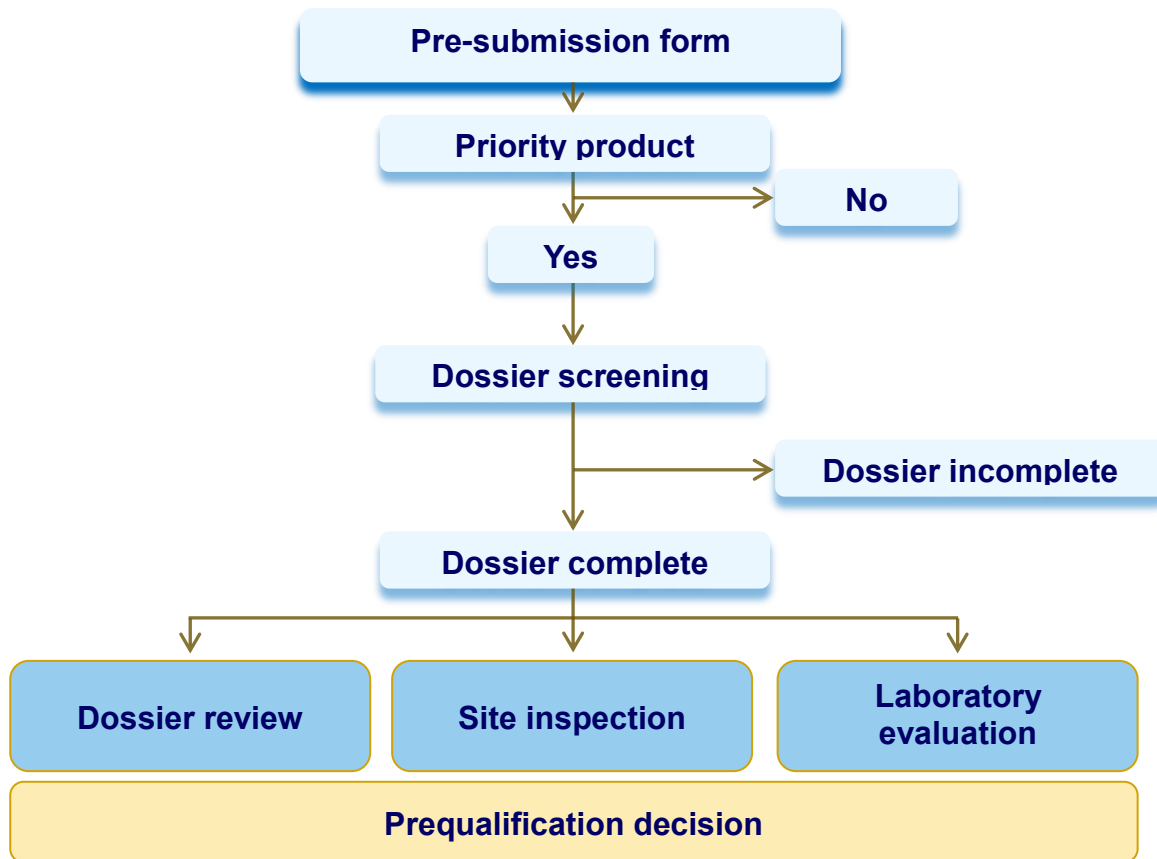


Figure 1 Prequalification of diagnostics: full assessment process

### 8.1. Product dossier review

WHO reviews the product dossier with the purpose of:

- Assessing evidence in support of safety and performance of the product;
- Assessing the product design and manufacture; and
- Determining if the manufacturer's quality management system is of an adequate standard to warrant an inspection of the manufacturing site.

The information submitted in the product dossier will be assessed by experts (assessors) appointed by WHO. Assessors involved in the product dossier review must have the qualifications and expertise in the relevant fields and must comply with the confidentiality and conflict of interest rules of WHO. The assessors will act as temporary advisers to WHO.

The assessment of product dossiers will be done in accordance with SOPs established by WHO for that purpose so as to ensure uniformity in evaluation and timeliness of assessment activities. If needed, WHO may provide training to the assessors.

Any deficiencies in the submitted documentation and/or data identified in the product dossier review will be communicated in writing to the manufacturer. A corrective action plan that details the amendments (i.e., responses to comments; documentation and/or data that is missing or may be requested) and timelines for their submission should be provided. The manufacturer will have

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the opportunity to submit up to two corrective action plans and, provided that the corrective action plan is accepted by WHO, only one amendment to the original product dossier will be permitted. The prequalification assessment procedure is usually suspended (i.e., WHO will not undertake any further action) until a corrective action plan has been submitted by the manufacturer and accepted by WHO.

Each manufacturer may request a hearing or meeting with the WHO experts involved in the assessment of the manufacturer's product dossier in order to clarify issues identified by the WHO experts. WHO may provide technical assistance to manufacturers regarding appropriate product information to be submitted as well as production and control requirements.

A summary of the product dossier review will be included in the WHO prequalification public report, if the product successfully meets the WHO prequalification requirements. If the product dossier does not meet WHO prequalification requirements or in the event any of the other conditions outlined under Section 10.3 is met, the prequalification application will be terminated.

## **8.2. Laboratory evaluation of the product**

The purpose of the laboratory evaluation is to evaluate the performance and operational characteristics of the product. Laboratory evaluation of the product occurs following a successful review of the product dossier, and it is carried out by specified WHO Collaborating Centre(s)<sup>5</sup> or designated laboratory(ies) (collectively "evaluating site(s)") under the instructions of WHO. The product will be evaluated against pre-determined performance criteria established by WHO.

Before commencement of the laboratory evaluation, the WHO evaluation protocol that outlines the procedures used to evaluate the product performance and operational characteristics will be sent to the manufacturer. The manufacturer will then be contacted by the relevant evaluating site(s) and requested to send sufficient quantities from at least two different lots<sup>6</sup> of the product. Detailed shipping instructions (e.g., number of test kits and/or instruments, number of lots, etc.) will be communicated in due time to the manufacturer by the evaluating site(s). The manufacturer should not send tests to the evaluating site(s) unless explicitly invited to do so.

The manufacturer must send to the evaluating site(s) the requisite quantities and lots of the product (test kits and/or instruments) Free Domicile, in accordance with the aforementioned detailed shipping instructions, free-of-charge, and delivered with all customs declarations, customs duties, and transport and other charges paid for by the manufacturer. If necessary, special equipment needed to perform the assay must be made available by the manufacturer at no charge (i.e. customs declaration and payment of customs duties, transport, installation, training, etc., shall be taken care of by the manufacturer) to the evaluating site for the duration of the prequalification assessment process.

WHO will have absolute, exclusive, unfettered control over the manner in which the prequalification assessment process is carried out (including the laboratory evaluation and/or the

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<sup>5</sup> WHO Collaborating Centres are institutions designated by the WHO Director-General to form part of an international collaborative network carrying out activities in support of the WHO's programme at all levels. In certain instances additional laboratories may be contracted by WHO to perform laboratory evaluation.

<sup>6</sup> For the purposes of WHO evaluation, a lot is defined as "The amount of material that is uniform in its properties and has been produced in one process or series of processes. The material can be either starting material, intermediate material or finished product." Furthermore, the two lots must be sourced from a representative production run and not produced especially for the purpose of the WHO evaluation.

publication of results of the prequalification assessment, regardless of the outcome). Without prejudice to the foregoing and in agreement with WHO, the manufacturer may wish to visit the specified evaluating site(s) to observe the operator performing the test procedure of the manufacturer's product(s) before commencing the laboratory evaluation. There should not, however, be any changes made to the test procedure as outlined in the instructions for use. If so, WHO must be notified, and the laboratory evaluation will be suspended.

The evaluating site(s) will submit a draft evaluation report to WHO. After verification, WHO will send the draft laboratory evaluation report to the manufacturer and give it the opportunity to review and comment on the report and results. Any comments submitted by the manufacturer in writing to WHO within one month after the manufacturer's receipt of the draft laboratory report will be duly considered by WHO; however, WHO will maintain full control over the data analysis, reporting of the laboratory evaluation results and the content of any publication thereof. After one month, the laboratory evaluation report will be considered as final, if no further comments are received.

A summary of the laboratory evaluation report will be included in the WHO prequalification public report, if the product successfully meets the WHO prequalification requirements. Irrespective of whether or not the product meets WHO prequalification requirements, a summary of the laboratory evaluation report will be published in a WHO composite report as part of the WHO technical series on the performance and operational characteristics of commercially available IVDs.

### **8.3. Manufacturing site inspection**

The inspection of the manufacturing site(s) is conducted to assess compliance of the manufacturer's quality management system and manufacturing practices with international standards, such as the quality management standard *ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes* and other relevant international standards and guidelines produced by GHTF and IMDRF. However, the WHO manufacturing site inspection will focus on the suitability of the implemented processes and procedures for the reliable supply of products to WHO Member States. Therefore, customer-related issues and, as such, issues that may be covered only in general terms in ISO 13485:2003 are inspected in detail. Importantly, the inspection will also verify the content of the product dossier through review of reports and raw data onsite, and interview of personnel involved. The manufacturer should carefully read the information set out in the WHO document "PDQ\_014 – Information for Manufacturers on the Manufacturing Site(s) Inspection."

The initial manufacturing site inspection will be performed in two stages. The stage 1 inspection, usually a desk audit<sup>7</sup>, will evaluate the documentation related to the quality management system to ensure readiness for the 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 manufacturer's quality management system 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.

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.

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<sup>7</sup> The stage 1 inspection may also be performed on-site.

The inspection team is composed of WHO staff and external experts (inspectors) appointed by WHO. The inspectors involved in the on-site(s) inspection must have the relevant qualifications and expertise in the relevant fields, must comply with the confidentiality and conflict of interest rules of WHO, and will act as temporary advisers to WHO. Representatives of the national regulatory authorities, procurement agencies and other WHO employees may accompany the inspection team to the manufacturing site(s) as observers or for training purposes. 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.

All nonconformities will have to be addressed by the manufacturer through suitable corrective actions. The manufacturer will have the opportunity to submit up to two corrective action plans. WHO will assess the provided information and decide if the corrective action plan can be accepted and if a follow-up inspection has to be conducted. Conformity with prequalification requirements will be established based on assessment of such information.

A summary of the manufacturing site(s) inspection will be included in the WHO prequalification public report, if the product successfully meets the WHO prequalification requirements. If the manufacturer does not meet WHO prequalification requirements or if any of the other conditions outlined in Section 10.3 are met, the prequalification application will be terminated.

Re-inspection may occur when required to ensure ongoing compliance with prequalification requirements. Re-inspections will typically occur every three to five years after the prequalification of a product, unless an earlier re-inspection is deemed necessary.

## 9. Abbreviated prequalification assessment

The rationale for abbreviated prequalification assessment is that a regulatory approval provides a level of assurance relating to the quality, safety and performance in countries where the product is approved, but it cannot always provide the same assurance when the product is used in other jurisdictions, including in resource-limited settings.

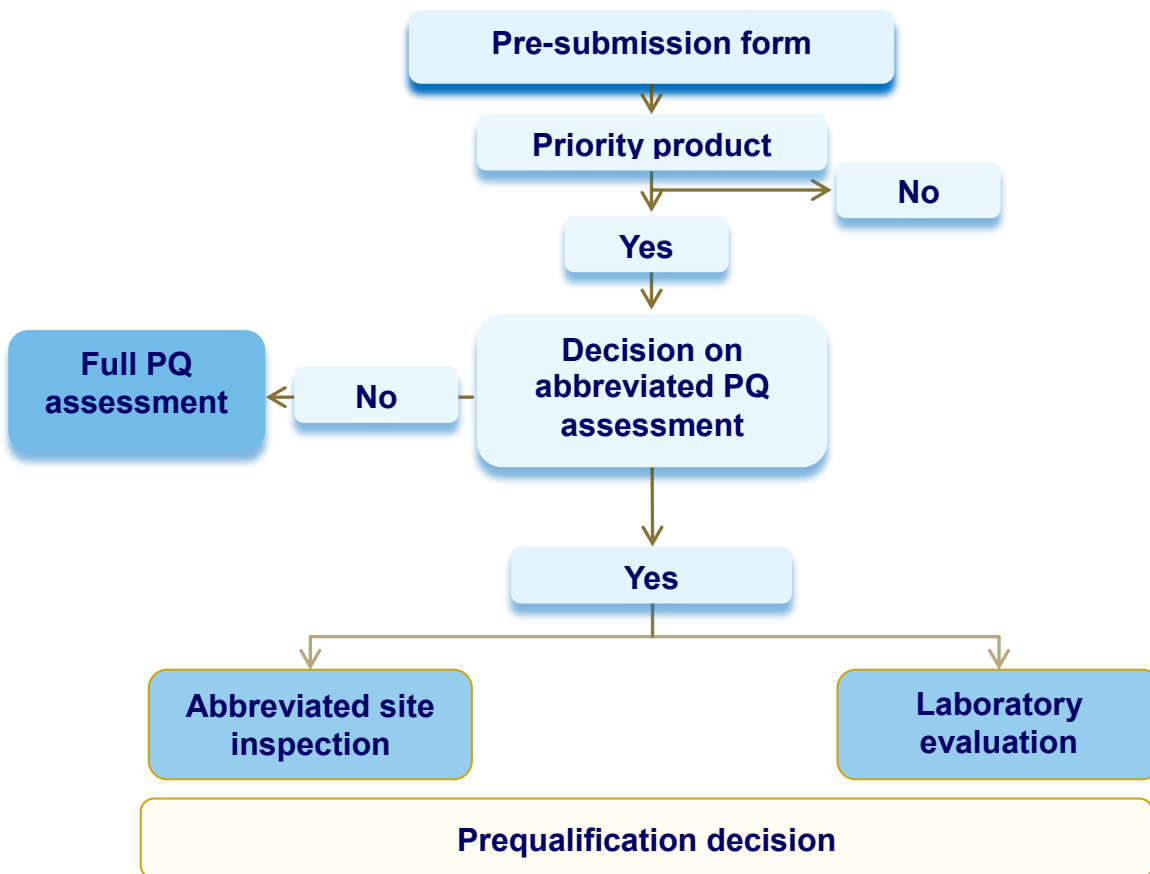
The aim of abbreviated prequalification assessment is to increase efficiencies, avoid duplication of effort and reduce the time to prequalify a product by focusing on aspects where WHO prequalification brings added value. WHO will review the pre-submission form and supporting documentation and then determine if the product is eligible for an abbreviated prequalification assessment. Products not eligible for abbreviated prequalification assessment will require a full prequalification assessment (refer to Section 8).

WHO will apply the abbreviated prequalification assessment, in accordance with WHO Document “PQDx\_173 – Abbreviated Prequalification Assessment”, in the following instances:

1. if a stringently assessed regulatory version is submitted for prequalification;
2. if a non-stringently assessed (rest of world) regulatory version of the product is submitted for prequalification assessment but a stringently assessed regulatory version also exists, and there are no substantial differences between the two regulatory versions.

The abbreviated prequalification assessment consists of two components (refer to Figure 2):

- Laboratory evaluation of performance and operational characteristics; and
- Abbreviated manufacturing site(s) inspection.



**Figure 2 Prequalification of diagnostics: abbreviated assessment process**

WHO will always undertake a laboratory evaluation of the product in the context of abbreviated prequalification assessment. The purpose of the laboratory evaluation is to independently evaluate the product performance on specimens from different geographical origins and address operational characteristics of major interest to resource-limited settings that would not have been addressed in the existing approval.

WHO will also always inspect the manufacturing site(s) to focus on the suitability of the implemented processes and procedures for the reliable supply of products to WHO Member States. All manufacturers are obliged to maintain a current technical file that demonstrates the quality, safety and performance for the product. However, for the abbreviated prequalification assessment, WHO will review certain elements during manufacturing site(s) inspection rather than through formal product dossier submission and review.

## 10. Outcome of the prequalification assessment

### 10.1. Successful prequalification

Once WHO is satisfied that the prequalification assessment process is complete for the relevant product, and that the product meets the WHO prequalification requirements, the product bearing a specific product name, product code(s) and regulatory version, as manufactured at the specific manufacturing site(s) inspected, will be included in the WHO list of prequalified IVDs. The WHO list of prequalified IVDs will be compiled in accordance with a standard operating procedure (SOP) established by WHO for final decision-making on inclusion in such list. The list will be published on the WHO website and will specify the prequalified product name, the respective product code(s), regulatory version, the manufacturer name, the manufacturing site(s), the product packaging and the year on which the product is prequalified.

The manufacturer will receive a letter of prequalification from WHO informing it of the outcome of the overall prequalification assessment of the product. Once the product is included in the WHO list of prequalified IVDs, the manufacturer will be responsible for: (i) keeping WHO continuously updated on all relevant aspects of the manufacture and control of the product, and on any changes to the product and/or the quality management system, as well as (ii) meeting any requirements as agreed with WHO.

The decision to list the product on the WHO list of prequalified IVDs is made based upon information available to WHO at the time of the prequalification assessment, including information obtained as a result of the product dossier review, laboratory evaluation and/or manufacturing site(s) inspection conducted by WHO. This decision is subject to change on the basis of new information that may become available to WHO.

NOTE: If serious quality, safety and/or performance concerns arise in relation to a product undergoing prequalification or a prequalified product, WHO reserves the right to issue a field safety notice or a notice of concern. Consequently, WHO may delist the product after evaluation of the evidence and risk-benefit assessment, or may suspend the product until results of further investigations become available and are assessed by WHO. WHO may relist the product only after the aforementioned evidence, risk-benefit and other assessments, and investigation results are considered acceptable by WHO.

Manufacturers must understand that it is not WHO's mandate to issue any approvals, certificates or licenses for diagnostics. This responsibility lies within the national regulatory authority of each country. Furthermore, WHO does not, as a matter of policy, endorse any specific commercial product over others. As mentioned above, the purpose of the WHO Prequalification of IVDs is to provide guidance to interested UN agencies and WHO Member States in their procurement decisions. In this regard, the results of the prequalification assessment, the participation in the WHO prequalification assessment process, the inclusion of any product in the WHO list of prequalified IVDs and/or the WHO name and emblem, may not be used by manufacturers or any other party for commercial and/or promotional purposes. WHO will not accept any liability or responsibility whatsoever for an injury, death, loss, damage or other prejudice of any kind that may arise as a result of or in connection with the procurement, distribution and use of any product as to which WHO has published the assessment results and/or which is included in the WHO list of prequalified IVDs.

## **10.2. Reporting and Communication of the Results of the Prequalification Assessment Process**

As part of the prequalification assessment process, WHO may share the manufacturer's application and related information with interested national regulatory authorities (NRAs), subject to WHO entering into an appropriate confidentiality undertaking with each such NRA. Furthermore, the outcome of any joint review of information by WHO and NRA(s) may be utilized by WHO, in its discretion, as part of the prequalification assessment process.

Each assessment and inspection team will finalize its reports according to the relevant SOPs and format established by WHO, describing the findings and including recommendations to the manufacturer.

The findings from the dossier assessment including, but not limited to, deficiencies of the documentation and information submitted, will be communicated in writing to the manufacturer requesting submission of the missing documentation and information, as appropriate.

The inspection report will be communicated in writing to the manufacturer. If any additional documentation or information is required, or if corrective action has to be taken by the manufacturer, WHO will postpone its decision on the acceptability of the manufacturing site(s) concerned until, as applicable: (i) such information has been provided by the manufacturer and evaluated by WHO, and/or (ii) such corrective action has been taken by the manufacturer and found satisfactory by WHO, in light of the specified standards.

As WHO is responsible for the prequalification assessment process, the ownership of the reports arising from or relating to the prequalification assessment process lies with WHO. Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any commercially sensitive confidential information of the manufacturer. "Confidential information" in this context means:

- Confidential intellectual property, know-how, and trade secrets (including, e.g. formulas, processes or information contained or embodied in a product, unpublished aspects of trademarks, patents, etc.); and
- Commercial confidences (e.g. structures and development plans of a company).

Subject to the protection of commercially sensitive confidential information, WHO will publish on the WHO website and make publicly available the following information throughout the prequalification assessment process:

- The names of products and manufacturers that have applied for prequalification, the product code(s) submitted for prequalification and the prequalification status of each application;
- A WHO prequalification public report summarizing prequalification assessment findings;
- Any negative outcomes of the prequalification assessment, including product alerts such as field safety notices, notices of suspension and/or notices of concern; and
- "Re-branding" arrangements including the recommendation that the two products should not be used in combination within the same testing algorithm.

Notwithstanding any of the foregoing, WHO reserves the right to share the results of the prequalification assessment process as well as the full assessment and 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, with the relevant authorities of any interested WHO Member State and with relevant intergovernmental organizations.

### **10.3. Termination of the prequalification assessment**

WHO reserves the right to terminate the prequalification assessment process for a specific product at any time/stage if:

- The product dossier does not contain all of the required information or does not meet WHO prequalification requirements; and/or
- The manufacturer is not able to, or fails to, provide the required or requested information within a specified time period; and/or
- The product does not meet the acceptance criteria for the laboratory evaluation; and/or
- The manufacturer is not able to, or fails to, to implement any corrective actions which WHO may require within in a specified time period; and/or
- The information supplied is inadequate to complete the prequalification assessment.

In this case, the manufacturer will not be eligible to re-apply for WHO prequalification assessment for a period of time determined by WHO, usually one year from date of notification of termination.

#### **10.4. Withdrawal from the prequalification assessment**

WHO provides the manufacturer with the right to withdraw specific product(s) from the prequalification assessment at any time/stage. In order to exercise such right of withdrawal, the manufacturer must provide WHO with prior written notice specifying the product(s) to be withdrawn.

### **11. Post-market surveillance of WHO prequalified IVDs**

A post-market surveillance system has been developed by WHO to monitor the ongoing compliance of WHO prequalified products with WHO prequalification requirements. The WHO post-market surveillance system includes proactive collection of information on quality, safety and performance of the product after it has been prequalified as well as reactive reporting for the notification and evaluation of complaints (including adverse events) enabling appropriate action to be taken<sup>8</sup>.

As soon as a product is accepted into the prequalification assessment process, and as long as such product is on WHO's list of prequalified IVDs, the manufacturer shall, as a condition of prequalification, follow the guidance contained in the WHO Document entitled "Post-Market Surveillance of In Vitro Diagnostics" and, in particular, comply with the manufacturer's obligations set forth in that document including, for example, to undertake the following post-market surveillance activities:

- To notify WHO of any post-market events relating to the product that have affected (or could have affected) the performance of the assay, safety of the person being tested, safety of users of this assay or safety of any person associated with the product, including:
  - All complaints (both administrative and technical, including serious, moderate and mild adverse events), which must be reported to WHO annually as a periodic summary report;
  - Any serious adverse effect, which should be reported to WHO within 10 days; and
  - Any moderate adverse event or any changes in the trend of mild adverse events, which should be reported to WHO within 30 days.
- WHO may request that the manufacturer provides further information relating to the complaint or event, including details regarding the preventive and correction actions taken;
- To activate the manufacturer's complaint reporting and vigilance system, to inform WHO of reportable adverse events, and to encourage end users to report on problems experienced with the use of the product.
- To notify WHO of all events which require field safety corrective actions such as withdrawal of products from sale or distribution, physical return of the product to the manufacturer, product exchange, destruction of the product, product modification(s) or additional advice provision to customers to ensure that the product continues to function as intended;
- To submit information on all complaints, including any field safety corrective actions, and recalls carried out in the previous calendar year as part of the mandatory annual summary reporting; and
- If required, to supply sufficient quantities of the prequalified product to WHO, or laboratories designated by WHO, free-of-charge and delivered duty paid, for post-market surveillance testing.

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<sup>8</sup> The WHO post-market surveillance system does not replace any national post-market surveillance requirements.

Any post-market events/complaints concerning a prequalified product that is communicated to WHO will be investigated. Depending on the nature of the event/complaint, WHO may notify the manufacturer, national regulatory authorities, relevant authorities of any interested WHO Member State and/or interested UN agencies of the event/complaint. Subject always to the protection of commercially sensitive information as referred to above, WHO shall be entitled to make vigilance reports and product alerts public. In addition, WHO reserves the right to share the results and reports of any investigation relating to a post-market event/complaint, and/or the full post-market surveillance report, including any drafts of the aforementioned reports and, subject to appropriate obligations of confidentiality, any confidential information to which WHO may gain access in the course of any of the foregoing, with the relevant authorities of interested WHO Member States and interested UN agencies or other relevant intergovernmental organizations.

## **12. Prequalification fees**

The cost of the activities required to assess IVDs for prequalification will be covered in part by the manufacturer. The non-refundable first and, if applicable, second prequalification fee will contribute to the costs associated with prioritization, product dossier screening and review, laboratory evaluation, manufacturing site(s) inspection, and dissemination of prequalification information.

Manufacturers should note that WHO reserves the right to decide, based on the prequalification assessment findings, whether a product meets the requirements to become prequalified. Therefore, payment of the prequalification fees does not guarantee that the product will be prequalified.

If assessment of a change (variation) to the product or to the quality management system is required (refer Section 3), the manufacturer may need to pay an additional fee.

## **13. Notification of changes to prequalified IVDs**

WHO prequalifies an in vitro diagnostic as it is submitted to and assessed by WHO at a particular point in time. In order to meet the prequalification requirements, the manufacturer must establish, maintain and implement a procedure for categorizing and documenting any changes to the product and/or the quality management system. This procedure must be available as part of the product dossier and during the manufacturing site(s) inspection.

Manufacturers of products included in the WHO list of prequalified IVDs must comply with the duties and responsibilities set out in WHO document “PQDx\_121 – Reportable Changes to a WHO Prequalified IVD” including, without limitation, the obligation to report to WHO:

- Changes to the prequalified product or its manufacture;
- Changes to the quality management system that the product was designed and manufactured under; and/or
- Other reportable administrative changes.

To determine if a change to the product, including its design, labelling and manufacture, or to the quality management system requires notification to WHO, the manufacturer should evaluate the potential effect this change may have on the safety, quality or performance of the product.

All reportable changes to a prequalified product require the manufacturer to submit WHO document “PQDx\_119 – WHO Notification Form for Changes to a Prequalified In Vitro Diagnostic” and supportive documentation to the WHO Prequalification of IVDs and, in some cases, a new prequalification application.



Manufacturers should communicate their intent to introduce a substantial change well in advance (i.e., early in the process of designing and validating the change) to allow sufficient time for WHO to assess the change prior to its implementation. WHO will not approve any changes without due assessment. Depending on the type of change, the assessment may also include a manufacturing site inspection(s).

Once the change notification form and supportive documentation are received by WHO, they will be screened for completeness and, provided all the required information is contained, they will undergo assessment. If any aspect of the change notification form and supportive documentation is incomplete, the manufacturer will be informed and requested to complete it within a specified time period set by WHO. In the event of non-compliance, the product may be removed from the list of prequalified IVDs.

WHO will inform the manufacturer in writing of the outcome of the WHO assessment of the change. The manufacturer will also be notified if WHO deems (based on the nature of the change and its potential impact on the quality, safety and /or performance of the product) that a manufacturing site(s) inspection and/or performance evaluation is also required.

Once WHO is satisfied that the prequalification change assessment of a product is complete and the overall findings demonstrate that the product continues to meet all WHO prequalification requirements, the WHO list of prequalified IVDs will be updated, as necessary, to reflect the relevant change accepted by WHO.

If the submitted documentation supporting supporting the change does not meet WHO prequalification requirements or the requested information is not provided by the manufacturer within the specified time period, WHO will reject the change. The impact of such a decision on the prequalification status of the prequalified IVD will be communicated to the manufacturer.

## **14. Validity of prequalification status**

WHO will reassess products included in the WHO list of prequalified IVDs and their associated manufacturing sites at intervals determined by WHO on a risk-based approach. If, as a result of this reassessment, it is found that a product and/or specified manufacturing site(s) no longer meets WHO requirements, such products will be removed from the list. Failure of a manufacturer to participate in the reassessment procedure will also lead to delisting.

### **14.1. Annual reporting**

Manufacturers must submit, for all prequalified products, an annual summary report that details sales data and all categories of complaints in a summarized form. The annual report, in the format prescribed by WHO, must be submitted every year following prequalification. The report should be submitted no later than by 28 February for the previous calendar year.

## **15. Confidentiality**

WHO, assessors, inspectors and the designated evaluating laboratories will treat all information to which they will gain access during the assessments, inspections and evaluations, or otherwise in connection with the discharge of their responsibilities in regard to this prequalification procedure, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

WHO, assessors, inspectors and the designated evaluating laboratories will take all reasonable measures to ensure that confidential information:

- Is not used for any purpose other than the assessment/inspection/evaluation activities described in this document; and
- Is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

WHO, assessors, inspectors and evaluating laboratories will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- Was known to them prior to any disclosure by or on behalf of WHO (including by the manufacturers); or
- Was in the public domain at the time of disclosure by or on behalf of WHO (including by the manufacturers); or
- Has become part of the public domain through no fault of theirs; or
- Has become available to them from a third party not in breach of any legal obligations of confidentiality; or
- Was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such confidential information; or
- Is required to be disclosed by law, provided that WHO shall in such case immediately notify the manufacturer in writing of such obligation and shall provide adequate opportunity to the manufacturer to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).

## **16. Conflict of interest**

Before undertaking the work, each external inspector and assessor will also (in addition to the above-mentioned confidentiality undertaking) be required to complete and sign the WHO Declaration of Interests form.

If, based on the above mentioned Declarations of Interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt 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, 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 provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to WHO before the inspection visit. 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 ten (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.

## 17. Disputes; Privileges and Immunities of WHO

In the event of any dispute or disagreement between the manufacturer and WHO arising from or relating to the prequalification assessment process, an SOP established by WHO for the handling of such disputes and disagreements will be followed to discuss and resolve the issue.

By virtue of WHO's status as a specialized agency of the United Nations, WHO, its officials and experts performing missions for WHO (including, e.g., the prequalification assessors and inspectors) enjoy privileges and immunities under national and international laws and conventions, including the Convention on the Privileges and Immunities of the Specialized Agencies, adopted by the General Assembly of the United Nations on 21 November 1947 (the "1947 Convention"). Nothing contained in or relating to this document or the prequalification assessment will constitute or be deemed as a waiver of any of the privileges or immunities which WHO, its officials and/or experts performing missions for WHO enjoy pursuant to the 1947 Convention or otherwise under any national or international law, convention or agreement, and/or as submitting WHO, its officials and/or experts aforesaid to any national court jurisdiction.

## 18. Relevant documents

The following documents provide information to guide the manufacturer through the requirements of the prequalification assessment:<sup>9</sup>

- Pre-Submission Form: Document PQDx\_015
- Instructions for Completion of the Prequalification of In-Vitro Diagnostics Pre-submission Form: Document PQDx\_017
- Instructions for Compilation of a Product Dossier: Document PQDx\_018
- Product Dossier Checklist : Document PQDx\_049
- WHO Prequalification of Diagnostics: Abbreviated Procedure: Document PQDx\_173.
- Information for Manufacturers on the Manufacturing Site(s) Inspection (Assessment of the Quality Management System): Document PQDx\_014
- Reportable changes to a WHO Prequalified IVD: Document PQDx\_121
- WHO Post-market surveillance of in vitro diagnostics: ISBN 978 92 4 150921 3

If a product progresses to the laboratory evaluation stage of the IVDs prequalification assessment process, the manufacturer will be provided with the WHO evaluation protocol prior to the commencement of the evaluation.

## 19. Contact information

Any inquiries regarding the Prequalification of IVDs should be addressed to: [diagnostics@who.int](mailto:diagnostics@who.int)

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<sup>9</sup> Some documents can be accessed through the following website: [http://www.who.int/diagnostics\\_laboratory/evaluations/en/](http://www.who.int/diagnostics_laboratory/evaluations/en/)  
Other documents are produced by the International Organization for Standardization. For further information see [www.iso.org](http://www.iso.org)