



OVERVIEW OF THE PREQUALIFICATION OF IN VITRO DIAGNOSTICS ASSESSMENT

*WHO Prequalification of In Vitro Diagnostics
Programme*

Table of Contents

page

1.	Introduction	3
2.	Intended audience	3
3.	Definitions	3
4.	Abbreviations	4
5.	About prequalification of IVDs and procurement	4
6.	Eligibility for prequalification of IVDs	5
6.1.	Original manufacturer	5
6.2.	"Re-branding" arrangements	5
7.	Applying for WHO prequalification	6
7.1.	Pre-submission form and supportive documentation	6
7.2.	Prioritization for prequalification	6
7.3.	Product dossier submission and screening	7
8.	Full prequalification assessment	7
8.1.	Product dossier review	8
8.2.	Laboratory evaluation of the product	9
8.3.	Manufacturing site inspection	10
9.	Abbreviated prequalification assessment	10
10.	Outcome of the prequalification assessment	11
10.1.	Successful prequalification	11
10.2.	Termination of the prequalification assessment	13
10.3.	Withdrawal from the prequalification assessment	13
11.	Post-market surveillance of WHO prequalified IVDs	13
12.	Prequalification fees	14
13.	Notification of changes to prequalified IVDs	14
13.1.	Notification of substantial changes	14
13.2.	Annual reporting of changes	15
14.	Validity of prequalification status	15
15.	Confidentiality	15
16.	Conflict of interest	16
17.	Relevant documents	16
18.	Contact information	16

1. Introduction

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

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

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

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

The findings of the WHO Prequalification of IVDs Programme¹ are used to provide independent technical information on safety, quality and performance of in vitro diagnostics, principally to other United Nations (UN) agencies but also to WHO Member States and other interested organizations. The WHO prequalification status, in conjunction with other procurement criteria, is used by UN agencies, WHO Member States and other interested organizations to guide their procurement of in vitro diagnostics.

2. Intended audience

This document has been prepared to provide manufacturers with an overview of the process for WHO prequalification assessment. It is recommended that manufacturers wishing to apply for WHO prequalification of their product(s) read this document before applying for prequalification. This will ensure 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 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	Review of product dossier, laboratory evaluation of performance

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.

assessment	and operational characteristics and site inspection.
in vitro diagnostic	A medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.
WHO laboratory evaluation	Laboratory-based evaluation of the performance and operational characteristics of a product for the purpose of WHO prequalification.
manufacturer	Any natural or legal person with responsibility for design and/or manufacture of a diagnostic product with the intention of making the diagnostic product available for use, under his/her name; whether or not such a diagnostic product is designed and/or manufactured by that person himself/herself or on his/her behalf by another person(s).
re-brander	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.
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
WHO	World Health Organization
UN	United Nations

5. About prequalification of IVDs and procurement

The goal of the WHO Prequalification of IVDs Programme is to improve access to IVDs that are safe, affordable, of good quality and performance, and are appropriate for use in resource-limited

settings. To this end, the WHO Prequalification of IVDs Programme provides information on the outcomes of the intermediate and final steps of the prequalification assessment process to UN agencies, WHO Member States, and other interested organizations to guide their procurement decisions.

To ensure that WHO can prequalify IVDs as efficiently as possible, it is expected that manufacturers will be fully prepared for prequalification assessment when they apply for WHO prequalification. Manufacturers may wish to contact the WHO Prequalification Team – Diagnostics Assessment (e-mail: 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 and other interested organizations are invited to use the WHO list of prequalified IVDs for procurement decisions.

6. Eligibility for prequalification of IVDs

6.1. Original manufacturer

Applications to the WHO Prequalification of IVDs Programme are only accepted from the legal manufacturer of the product.²

6.2. "Re-branding" arrangements

WHO is aware that several manufacturers purchase finalized and semi-finalized products from other companies and then "re-brand" these products and place them 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.

² 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/>

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 “PQDx_017 Instructions for the Completion of the 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 the product submitted for prequalification or not.

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 notification to WHO. Any changes to such version must be agreed with 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 Programme prioritization criteria:³

- 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 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.

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

³ 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.

The pre-submission form and supportive documentation will be reviewed against the above WHO Prequalification of IVDs Programme 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 the WHO document "PQDx_018 Instructions for Compilation of a Product Dossier". Manufacturers should not submit a product dossier or pay fees unless instructed to do so by WHO.

The content of the product dossier should be consistent with the information submitted in the pre-submission form and 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. 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 and requested to provide supplements within a specified time period. There will be two opportunities to submit the required supplemental information before the application will be terminated. The application will be terminated if the product dossier does not contain all the required information, or where the submission timelines set by WHO are not met.

Once the product dossier is determined to be complete, a second fee will be levied before the prequalification assessment can commence.

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.

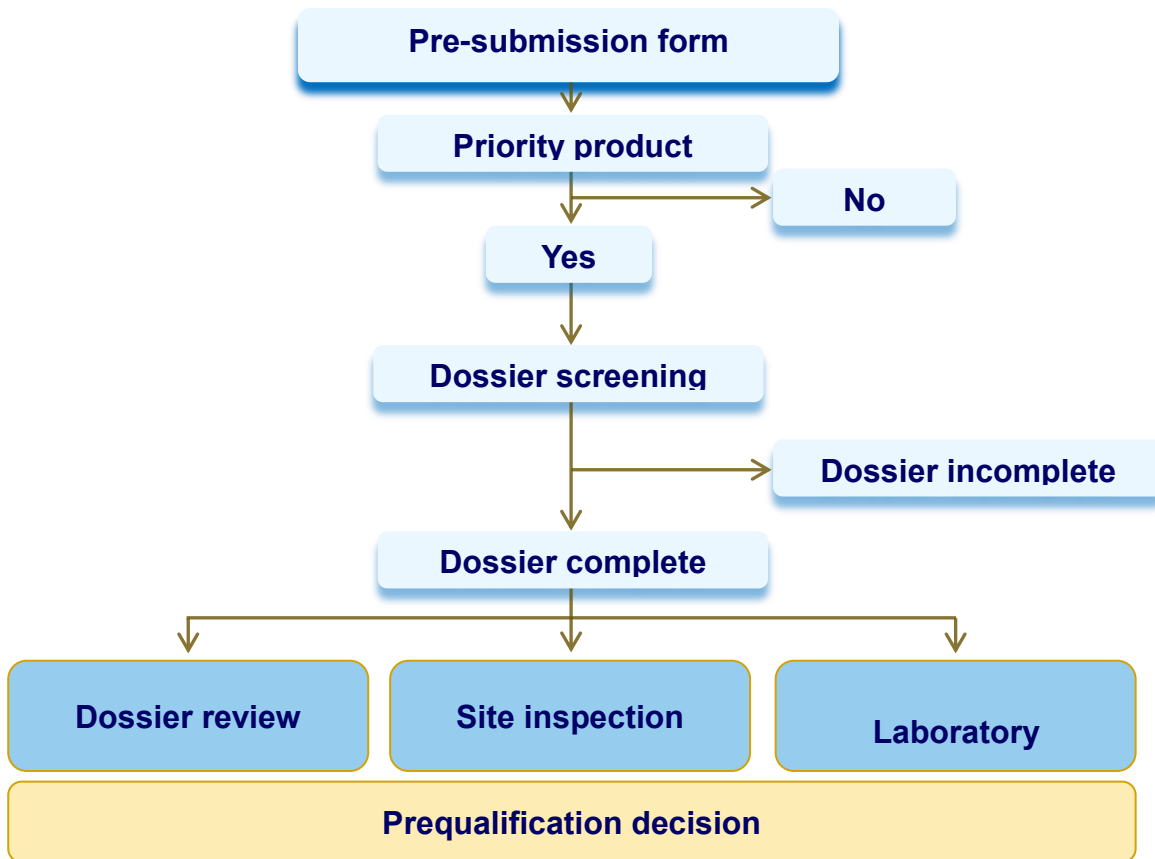


Figure 1 Prequalification of diagnostics: full assessment process

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 external experts (assessors) appointed by WHO. Assessors must have the qualifications and expertise in the relevant fields and must comply with the confidentiality and conflict of interest rules of WHO.

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 (missing documentation and/or data) and timelines for their submission should be provided. The manufacturer will have 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.

A summary of the 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 where the requested information is not provided by the manufacturer within a specified time period, 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 and is carried out by specified WHO Collaborating Centre(s)⁴ or designated laboratory(ies) 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 forwarded 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 lots⁵ of the product, provided at no charge to the evaluating site(s). The manufacturer should not send tests to the evaluating site(s) unless explicitly invited to do so.

The product (test kits and/or instruments) shall be sent Free Domicile, and detailed shipping instructions shall be communicated in due time to the manufacturer by the evaluating site, e.g. number of tests, number of lots and must be sent free-of-charge and delivered duty paid. If necessary, special equipment needed to perform the assay shall be made available by the manufacturer at no charge to the evaluating site for the duration of the prequalification assessment i.e. customs declaration and payment of customs duties, transport, installation, training, etc., shall be taken care of by the manufacturer.

WHO will have absolute unfettered control over the manner in which the laboratory evaluation is carried out. 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 their product(s) before commencing the evaluation. There should not, however, be any changes made to the test procedure as outlined in the instructions for use. If so, WHO should 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 them the opportunity to review and comment on the report and results. Any comments 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 if the product meets WHO prequalification requirements or does not, 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.

⁴ 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.

⁵ 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.

8.3. Manufacturing site inspection

The inspection of the manufacturing site(s) is conducted to assess compliance with the quality management standard *ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes* and with other relevant international standards and guidelines produced by the GHTF and IMDRF. However, the WHO 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 stage 1 inspection, usually a desk audit⁶, will evaluate the documentation related to the quality management system to ensure readiness for a stage 2 inspection. 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 quality management system and implemented production processes through a site(s) inspection. The inspection team is composed of WHO staff and external experts (inspectors) appointed by WHO. The inspectors must have the relevant qualifications and expertise in the relevant fields and must comply with the confidentiality and conflict of interest rules of 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 where the requested information is not provided by the manufacturer within a specified time period, the prequalification application will be terminated.

Re-inspection may occur, when required to ensure ongoing compliance with prequalification requirements.

9. Abbreviated prequalification assessment

The aim of abbreviated prequalification assessment is to avoid duplication of effort and to reduce the time to prequalify a product. WHO will review the pre-submission form and supportive documentation and then determine if the product is eligible for an abbreviated prequalification assessment.

⁶ The stage 1 inspection may also be performed on-site.

WHO will apply the 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.

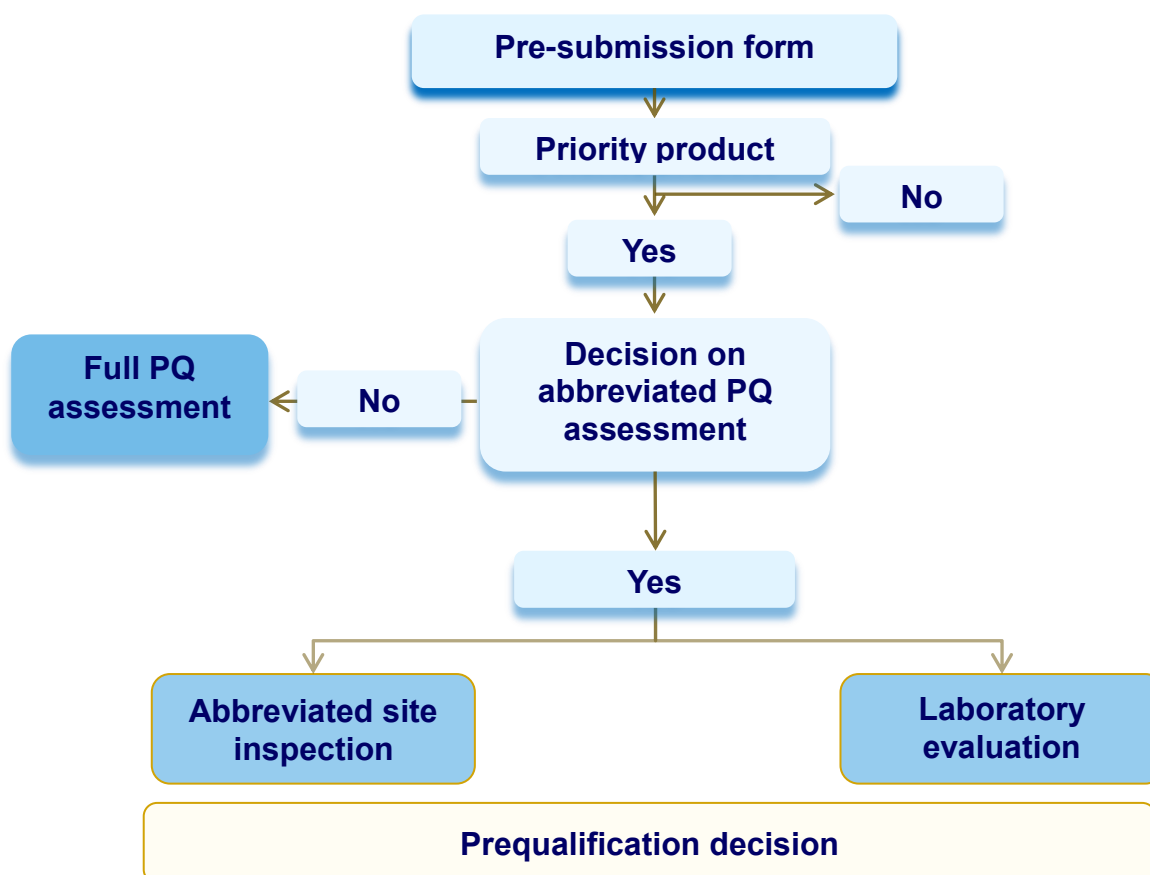


Figure 2 Prequalification of diagnostics: abbreviated assessment process

A regulatory approval does provide 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. WHO will always undertake a laboratory evaluation of the product and inspect the manufacturing site(s). 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 inspection rather than through formal dossier submission and review.

10. Outcome of the prequalification assessment

10.1. Successful prequalification

Once 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 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 and address and the product packaging. In addition, a WHO prequalification public report summarizing the prequalification assessment findings will be made publicly available.

The manufacturer will receive a letter from WHO informing them of the outcome of the overall assessment of the product. Once the product is included in the WHO list of prequalified IVDs, the manufacturer will be responsible for keeping WHO updated on changes to the product and the quality management system.

The decision to prequalify the product is made based upon information available to WHO at the time of the prequalification assessment including product dossier review, laboratory evaluation and 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 there is evidence of serious quality, safety and/or performance issues in relation to product undergoing prequalification or a prequalified product, WHO reserves the right to issue a field safety notice or a notice of concern. Consequently, delisting of the product may occur until results of further investigations become available and are assessed by WHO and considered acceptable. At such time, WHO may relist the product.

Manufacturers should understand that it is not WHO's mandate to issue 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. In addition, in keeping with WHO policy, the results of the prequalification assessment, the participation in the WHO prequalification, the inclusion in the WHO list of prequalified IVDs or the WHO name and emblem, should 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.

- As WHO is responsible for the prequalification process, the ownership of the reports 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, programs, 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 always to the protection of commercially sensitive confidential information, WHO will in particular make publicly available the following information throughout the prequalification process (manufacturers should note that WHO shall also be entitled to publish negative assessment outcomes): The names of products and manufacturers that have applied for prequalification, the product code(s) codes submitted for prequalification and the prequalification status of each application;
- A WHO prequalification public report summarizing prequalification assessment findings;
- Any product alerts such as field safety notices 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.

10.2. Termination of the prequalification assessment

WHO reserves the right to terminate the prequalification assessment at any time/stage if:

- The manufacturer is not able to, or fails to, provide the required information; and/or
- The product does not meet the acceptance criteria for the laboratory evaluation; and/or
- The manufacturer is unable to implement any corrective actions which WHO may require in a specified time period; and/or
- The information supplied is inadequate for effective 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.

10.3. Withdrawal from the prequalification assessment

WHO provides the manufacturer with the right to withdraw from the prequalification assessment at any time/stage.

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 taken⁷.

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 agree, as a condition of prequalification, to undertake the following post-market surveillance activities:

- To notify WHO of all adverse 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. WHO may request that the manufacturer provides further information relating to the event, including details regarding the preventive and correction actions taken;
- 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 recalls carried out in the previous calendar year as part of the mandatory annual 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.

Any events/complaints concerning a prequalified product communicated to WHO will be investigated. Depending on the nature of the event/complaint, WHO may notify the manufacturer and national regulatory authorities 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

⁷ The WHO post-market surveillance system does not replace any national post-market surveillance requirements.

entitled to make vigilance reports and product alerts public. In addition, WHO reserves the right to share the full post-market surveillance report with the relevant authorities of interested Member States of the Organization and interested UN agencies.

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 second prequalification fees 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. WHO also reserves the right to terminate the prequalification assessment process at any stage if the manufacturer is not able to, or fails to, provide the required information in a specified time period, or when the information supplied is inadequate to complete the prequalification assessment effectively.

If assessment of a change (variation) to the product or to the quality management system is required (refer Section 14), 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 should establish, maintain and implement a procedure for categorizing and documenting any changes to the product and/or the quality management system. This procedure should be available as part of the product dossier and during the site(s) inspection.

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.

13.1. Notification of substantial changes

Substantial changes to a prequalified product require the submission of a WHO change notification form and supportive documentation to the WHO Prequalification of IVDs Programme.

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. In the event of non-compliance, the product may be removed from the list of prequalified IVDs.

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 respective change.

13.2. Annual reporting of changes

Manufacturers must submit, for all prequalified products, annual reports listing all changes implemented during the calendar year. These will include minor and substantial changes, administrative changes and any other changes implemented by the manufacturer.

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.

WHO will review the list of changes implemented by the manufacturer. The manufacturer may be requested to submit additional information supporting any of the notified changes. If the information supplied by the manufacturer is inadequate or where the requested information is not provided by the manufacturer within a specified time period, the product may be removed from the list of prequalified IVDs.

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 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.

15. Confidentiality

The assessors, inspectors and the designated evaluating sites carrying out the laboratory evaluation 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 procedure, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

Assessors, inspectors and evaluating sites 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.

Assessors, inspectors and evaluating sites 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 the manufacturers); or
- Was in the public domain at the time of disclosure by or on behalf of WHO (including 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.

16. Conflict of interest

Prior to formalizing arrangements with external inspectors and assessors, WHO will also (in addition to the above-mentioned confidentiality undertaking) require each of them 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), the aforesaid experts will discharge their functions exclusively as advisers to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed is correct and complete, and that he/she will immediately notify WHO of any change in this information.

17. Relevant documents

The following documents provide information to guide the manufacturer through the requirements of the prequalification assessment:⁸

- Instructions for Completion of the Pre-submission Form: Document PQDx_017
- Pre-Submission Form: Document PQDx_015
- 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 Prequalification Inspection Procedures for the Sites of Manufacture of Diagnostics - Document PQDx_014
- ISO 13485:2003 Medical devices - Quality management systems - Requirements for regulatory purposes.
- ISO/TR 14969 Medical devices - Quality management systems - Guidance on the application of ISO 13485.

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

18. Contact information

Any inquiries regarding the Prequalification of IVDs Programme should be addressed to: diagnostics@who.int

⁸ Some documents can be accessed through the following website: 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