Public consultation on proposed revisions to the WHO Prequalification of in vitro diagnostics assessment process

1. Introduction

The World Health Organization's (WHO) prequalification of in vitro diagnostics ("IVDs" or "product(s)") is a comprehensive quality assessment of individual IVDs through a standardized procedure aimed at determining whether a product meets WHO prequalification requirements.

In light of the growing need for increased access to quality assured IVDs in low and middle-income countries, and of the increasing volume of new applications and change requests relating to WHO's prequalification assessment of a broad range of IVDs, WHO has identified the need to review/revise the WHO prequalification processes for IVDs and to identify opportunities for increased efficiency while preserving the quality of such assessments.

In this context, proposed revisions to the WHO prequalification assessment process for IVDs (under both the full and abridged pathways) have been identified and are presented in this document.

WHO is seeking for public comments on the abovementioned proposed revisions. The manner and deadline for submitting comments is set forth in Section 7 below.

2. Acronyms

As used in this document, the following acronyms apply:

DOS	Product Dossier Review
ED-PE	Eligibility decision by WHO on whether or not the product is eligible for performance evaluation
ED-PQ	Eligibility decision by WHO on whether or not the product is eligible for WHO prequalification assessment
EOI	Performance evaluation expression of interest form
ePQS	Entry by the manufacturer of all required information on the product and manufacturing site in the ePQS system[1]
FEE	Payment of PQ fees
INS	Manufacturing site inspection
LoA	Letter of Agreement for PQ
LR	Labelling review
PE	Performance evaluation
PEA	Performance evaluation Agreement
PED	Decision by WHO whether or not the performance evaluation results are acceptable to WHO (i.e., whether or not the PE has been successfully completed)

[1] IT platform used by WHO to manage prequalification information

PEF	Payment of performance evaluation fee to the evaluating laboratory
PEPAR	Performance Evaluation Public Assessment Report
PQ	WHO Prequalification of In Vitro Diagnostics
PQD	Decision by WHO whether or not to prequalify a product
PSF	Pre-submission form and related supporting/additional documentation
WHO	World Health Organization
WHOPAR	WHO Public Assessment Report

3. Background

As mentioned above, WHO's prequalification of IVDs is a comprehensive quality assessment of individual IVDs through a standardized procedure aimed at determining whether a product meets WHO prequalification requirements.[2]

The full prequalification assessment includes the following four components:

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

The abridged prequalification assessment includes the following four components:

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

Products submitted for prequalification assessment that meet, as determined by WHO, the WHO prequalification requirements are included in the WHO list of prequalified IVDs. The findings of WHO prequalification 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.

4. Brief high-level description of current process for WHO prequalification of IVDs

WHO prequalification of IVDs has been implemented since 2010. The current prequalification process has been in place since 2014 and is briefly summarized and presented in Figure 1 below.

[2] For further information on WHO's Prequalification of IVDs, please refer to the OVERVIEW OF THE PREQUALIFACTION ASSESSMENT PROCEDURE (who.int)

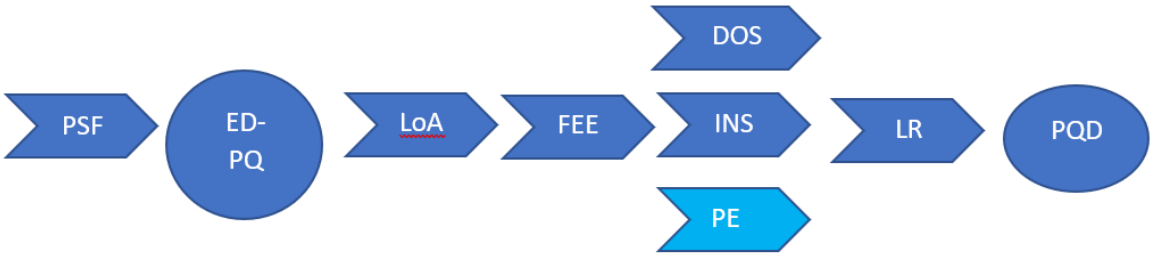

Figure 1. Current process for WHO prequalification of IVDs

DOS: product dossier review; ED-PQ: eligibility decision by WHO on whether or not the product is eligible for WHO prequalification assessment; FEE: Payment of PQ fees; INS: manufacturing site inspection; LoA: Letter of Agreement for PQ; LR: labelling review; PE: performance evaluation; PQD: decision by WHO whether or not to prequalify a product; PSF: pre-submission form and related supporting/additional documentation.

Under the current processes, the manufacturer must complete and submit to WHO a pre-submission form and all requested supporting/additional documentation. The aforementioned form and documentation are reviewed by WHO against relevant eligibility criteria so that WHO can determine whether or not the product in question is eligible for prequalification assessment and, if so, whether or not the prequalification assessment can be abridged.

If WHO determines that a product is eligible for prequalification assessment, the manufacturer must sign and return to WHO the Letter of Agreement (in the form provided by WHO), which will serve: (i) as an agreement between WHO and the manufacturer on the participation of the product in the prequalification assessment process, and (ii) as the manufacturer's acceptance of, and commitment to comply with, the provisions of the prequalification assessment process. Applicable prequalification fees will also be payable by the manufacturer to WHO at this stage.

Before the prequalification assessment of an eligible product can commence, the manufacturer must submit and deliver to WHO: (i) a duly completed and signed Letter of Agreement, and (ii) proof of payment of the prequalification fee, and (iii) the relevant product dossier. Once the product dossier has been received by WHO, it undergoes screening for completeness.

If the product dossier is complete (as determined by WHO), the four main components of the prequalification assessment (namely a product dossier assessment, manufacturing site inspection, a performance evaluation (which is further described under Section 4 below) and labelling review) will then be undertaken by WHO. The product dossier assessment, manufacturing site inspection and performance evaluation are scheduled first and implemented concurrently. If and when the three assessment components are successfully completed (i.e., successfully meet the applicable WHO prequalification requirements), then the labelling review takes place.

After labelling review is complete, WHO makes a decision (taking into account the outcomes of each assessment component) on whether or not to prequalify the product in question. For a product to be prequalified, WHO must be satisfied that the product meets all WHO

prequalification requirements in all assessment components. If a product is prequalified, it will be included in WHO's list of prequalified IVDs provided, among other things, that the manufacturer timely fulfills all post-prequalification commitments.

5. Brief high-level description of performance evaluations under the current procedure for WHO prequalification of IVDs

The performance evaluation is essential for independent verification of the performance and operational characteristics of IVDs submitted for prequalification. The data obtained complement the verification and validation data submitted by the manufacturer in the product dossier.

Under the current procedure for WHO's prequalification assessment of IVDs, the performance evaluation is one of the four main components of such prequalification assessment (both full and abridged). The performance evaluation of the product is carried out by specified WHO collaborating centre(s) or a designated laboratory or laboratories (collectively referred to as "evaluating site(s)"), using the WHO prequalification evaluation protocol.

The manufacturer must choose one of the following two performance evaluation options:

- *Option 1: Performance evaluation commissioned by WHO and carried out at an evaluating site listed by WHO.* If this option is chosen, WHO pays the evaluating site for the performance evaluation, provided however that the manufacturer has first paid the prequalification fee to WHO. WHO will commission and coordinate the performance evaluation with the evaluating site. The evaluating site will conduct the performance evaluation and share the data from the evaluation directly with WHO.

- *Option 2: Performance evaluation commissioned by the manufacturer and carried out at an evaluating site listed by WHO*. If this option is chosen, the manufacturer is responsible for: (a) commissioning the performance evaluation directly with an independent laboratory selected by the manufacturer from the list of evaluating sites, and (b) paying the full cost of the performance evaluation (in addition to paying the applicable prequalification assessment fee), and (c) coordinating the performance evaluation directly with the evaluating site. The evaluating site will conduct the performance evaluation and share the data arising therefrom directly with WHO and the manufacturer.

Under both options 1 and 2, the performance evaluation is implemented (in accordance with a standardized WHO evaluation protocol) in one or several evaluating site(s) listed by WHO for this activity.

WHO reviews the data analysis and draft performance evaluation report provided by the evaluating site and invites the manufacturer to review and provide comments on such draft report. WHO will reasonably consider the manufacturer's comments to the draft performance

evaluation report, provided that such comments are submitted in writing to WHO within one month after the manufacturer's receipt of the draft performance evaluation report. WHO then finalizes the performance evaluation report.

If the product successfully meets WHO prequalification requirements, a summary of the performance evaluation report will be included in the WHOPAR. If the product fails to meet WHO prequalification acceptance criteria for performance evaluations, the application will be terminated.

6. Proposed revisions to WHO's prequalification assessment (full and abridged) of IVDs: Successfully completed performance evaluation of a product as a pre-requisite to apply for WHO prequalification assessment of that product

As mentioned in Section 1 above, WHO has identified the need to review/revise the WHO prequalification processes for IVDs and to identify opportunities for increased efficiency while preserving the quality of such assessments.

The proposed revisions to the process are described in this Section 6 and briefly presented in Figures 2 and 3 below.

Under the proposed revised process, the successful completion (as further described below) of a performance evaluation of an IVD becomes a pre-requisite for a manufacturer to apply for WHO prequalification assessment of that IVD. Under this scenario, the performance evaluation of an IVD is a separate process from, and a pre-requisite to (as opposed to a component of), the WHO prequalification assessment of IVDs.

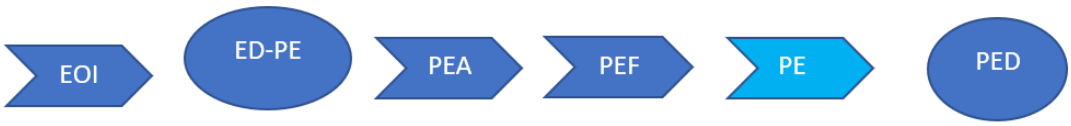

Figure 2. Performance evaluation as a pre-requisite to WHO PQ assessment

EOI: Performance evaluation expression of interest form; ED-PE: eligibility decision by WHO on whether or not the product is eligible for performance evaluation; PEA: performance evaluation agreement; PEF: payment of performance evaluation fee to the evaluating laboratory; PE: performance evaluation; PED: decision by WHO whether or not the performance evaluation results are acceptable to WHO (i.e. whether or not the PE has been successfully completed)

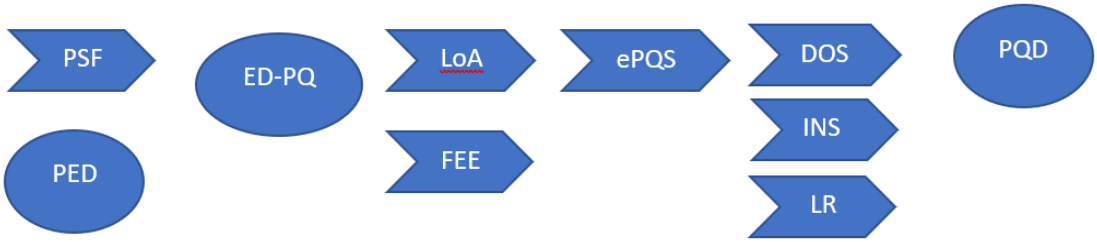

Figure 3. PQ assessment following successfully completed performance evaluation

DOS: product dossier review; ED-PQ: eligibility decision by WHO on whether or not the product is eligible for prequalification assessment; ePQS: Entry by the manufacturer of all required information on the product and manufacturing site in the ePQS system; FEE: Payment of PQ fees; INS: manufacturing site inspection; LoA: Letter of Agreement for PQ; LR: labelling review; PQD: decision by WHO whether or not to prequalify a product; PSF: pre-submission form and related supporting/additional documentation.

A. Performance Evaluation as a Pre-Requisite to Apply for WHO Prequalification Assessment of an IVD

Before a manufacturer may apply for a product to be assessed under WHO's prequalification procedure for IVDs, that product must first undergo and successfully complete a performance evaluation. The performance evaluation must be carried out by a WHO-listed evaluating site subject to and in accordance with: (i) the terms and conditions of WHO's procedure for performance evaluations; (ii) the WHO performance evaluation protocol; (iii) WHO guidance on performance evaluations; (iv) the terms and conditions of the agreement(s) relating to performance evaluations to be entered into by WHO and each such evaluating site; and (v) any other documents and/or information determined by WHO (all of the foregoing, collectively, the "PE Documents").

As a first step, the manufacturer must submit to WHO an Expression of Interest form, using the template to be provided by WHO for that purpose indicating its interest for a particular product to undergo a performance evaluation as a pre-requisite for WHO prequalification assessment (hereinafter, the "PE-EOI Form"). Once a complete PE-EOI Form and supporting documentation have been received by WHO, the Organization will review them against eligibility criteria established by WHO to determine whether or not the product in question is eligible for performance evaluation. WHO will inform the manufacturer in writing whether or not the product is eligible for performance evaluation.

If a product is found by WHO to be eligible for performance evaluation, WHO will request the manufacturer to complete, sign and return to WHO a Performance Evaluation Agreement (in the form provided by WHO) (hereinafter, the "PEA"), which will serve as: (i) an agreement between WHO and the manufacturer concerning the performance evaluation to be undertaken in respect of the product; and (ii) the manufacturer's acceptance of, and commitment to comply with, the terms and conditions of WHO's performance evaluation procedure. In addition, the manufacturer will be responsible for paying the full cost of the performance

evaluation either directly to the selected evaluating site or to WHO, depending on whether option 1 or option 2 is chosen, and no liability or obligation shall attach to WHO in this regard.

The manufacturer must choose one of the following two performance evaluation options:

- *Option 1: Performance evaluation commissioned by WHO and carried out at an evaluating site listed by WHO.* If this option is chosen, the manufacturer will be responsible for paying directly to WHO an amount equal to: (i) the full cost of the performance evaluation, and (ii) the associated WHO coordination cost, as determined by WHO. Provided that the aforementioned amount has been fully paid by the manufacturer to WHO, WHO will commission and coordinate the performance evaluation with the WHO-listed evaluating site selected by WHO. The evaluating site will conduct the performance evaluation in accordance with the PE Documents, and will share the data arising from the evaluation directly with WHO.

- *Option 2: Performance evaluation commissioned by the manufacturer and carried out at an evaluating site listed by WHO*. If this option is chosen, the manufacturer will be responsible for: (a) commissioning the performance evaluation directly with WHO-listed evaluating site selected by the manufacturer; and (b) paying the full cost of the performance evaluation directly to the evaluating site; and (c) coordinating the performance evaluation directly with the evaluating site. The manufacturer must require the evaluating site to, and the evaluating site must, conduct the performance evaluation in accordance with the PE Documents and share the data arising from the performance evaluation directly with WHO and the manufacturer.

Under both options 1 and 2, the performance evaluation is implemented by one or several evaluating site(s) listed by WHO for this activity, subject to and in accordance with the PE Documents. For specific product types, only option 1 may be available; in this case the manufacturer must follow option 1.

For the avoidance of doubt, the performance evaluation of a product shall not commence unless and until the manufacturer has delivered to WHO: (i) a duly completed and signed PEA, and (ii) where applicable (i.e., for option 1 above), payment of the performance evaluation fee and of the associated WHO coordination cost.

After the PEA has been fully completed, signed and returned to WHO by the manufacturer, WHO (if option 1 has been chosen) or the manufacturer (if option 2 has been chosen) may proceed to commission the performance evaluation directly with the selected WHO-listed evaluating site. If option 2 is chosen, the manufacturer and the evaluating site must ensure that the performance evaluation is carried out subject to and in accordance with the PE Documents.

Once the performance evaluation has been completed, the evaluating site must share directly

with WHO: (a) all data, analyses, findings and results arising from and/or relating to the performance evaluation (collectively, "PE Results"), as well as (b) a draft report of the performance evaluation in question (the "Draft PE Report"). WHO will review all the foregoing and, thereafter, will request the manufacturer to review and comment on the Draft PE Report. WHO will reasonably consider any comments by the manufacturer to the Draft PE Report, provided that such comments are submitted by the manufacturer in writing to WHO within one month after the manufacturer's receipt of the Draft PE Report. After such one-month period, the Draft PE Report will be considered as final.[3]

Once the performance evaluation has been completed and the PE Report has been finalized, WHO will decide whether or not the manufacturer's claims regarding the product are verified (to WHO's satisfaction) in accordance with WHO's performance evaluation protocol. If WHO determines that the manufacturer's claims regarding the product are verified (to WHO's satisfaction) in accordance with WHO's performance evaluation protocol, then:

- WHO will inform the manufacturer in writing that the product has "successfully completed" the performance evaluation; and
- WHO will publish a summary of the performance evaluation report; and
- The product will be eligible to apply for WHO prequalification of IVD assessment, subject to and in accordance with the provisions of that procedure (*NB: those provisions will also need to be revised in light of this proposed new process*).

If, on the other hand, WHO determines that the manufacturer's claims regarding the product are not verified (to WHO's satisfaction) in accordance with WHO's performance evaluation protocol, then:

- WHO will inform the manufacturer in writing of the same; and
- The product in question will not be allowed to apply for WHO prequalification assessment; and
- The product in question will not be allowed to re-apply for performance evaluation, unless and until all of the following conditions have been met:
    - A design change in respect of the product and its performance has been implemented by the manufacturer (the "Design Change"); and
    - The manufacturer has submitted to WHO the Design Change and the supporting documentation requested by WHO, for WHO's review; and

[3] For the avoidance of doubt, consistent with all established Prequalification and Emergency Use Listing procedures adopted by WHO, WHO will maintain full and exclusive control over all analyses, reports and/or publications arising from or relating to the performance evaluation and/or the PE Results. As the performance evaluation is a pre-requisite to WHO's prequalification of IVDs, the ownership of any analyses, reports and/or publications arising from or relating to the performance evaluation will lie exclusively with WHO. Accordingly, WHO shall be entitled to use, share and publish such analyses, reports and/or materials in its discretion, subject to the protection of any confidential information of the manufacturer.

- WHO has reviewed the submitted Design Change and the supporting documentation and has informed the manufacturer in writing that the product in question is allowed to be re-submitted for performance evaluation.

Irrespective of the outcome of the performance evaluation (e.g., irrespective of whether WHO determines that the manufacturer's claims regarding the product are or are not verified (to WHO's satisfaction) in accordance with WHO's performance evaluation protocol a summary of the results of the performance evaluation will be published by WHO in the performance evaluation public assessment report (PEPAR). In addition, the results of the performance evaluation may be published by WHO in a WHO composite report as part of the WHO technical specification series on the performance and operational characteristics of commercially available IVDs or in an article in a scientific journal.

B. WHO Prequalification Assessment of IVDs, only if and after a performance evaluation of the product has been successfully completed

An application for WHO prequalification of IVDs will not be accepted by WHO unless and until a performance evaluation (as described under part A above) of the product has first been "successfully completed" (i.e., WHO has determined that the manufacturer's claims regarding the product are verified (to WHO's satisfaction) in accordance with WHO's performance evaluation protocol). Applications for WHO prequalification assessment of an IVD will not be accepted by WHO if the performance evaluation has not been commenced, is ongoing or pending, and/or has failed to be successfully completed (as determined by WHO).

If an IVD has successfully completed a performance evaluation and the manufacturer wishes to apply for WHO prequalification assessment of that product, then the manufacturer must submit an application for prequalification assessment by: (a) completing and submitting to WHO a pre-submission form, and (b) providing to WHO all requested supporting/additional documentation which will include, among other things, proof that the product in question has "successfully completed" a performance evaluation (see Part A above). The pre-submission form and supporting/additional documentation are reviewed by WHO against relevant eligibility criteria so that WHO can determine whether or not the product in question is eligible for prequalification assessment and, if so, whether or not the prequalification assessment can be abridged.

If WHO determines that a product is eligible for prequalification assessment, the manufacturer must complete, sign and return to WHO the Letter of Agreement (in the form provided by WHO), which will serve: (i) as an agreement between WHO and the manufacturer on the participation of the product in the prequalification assessment process, and (ii) as the manufacturer's acceptance of, and commitment to comply with, the provisions of the prequalification assessment process. At this stage, the manufacturer must also pay WHO the applicable prequalification fees.

Before the prequalification assessment of an eligible product can commence, the manufacturer must submit and deliver to WHO: (i) a duly completed and signed Letter of Agreement, and (ii) proof of payment of the applicable prequalification fees. In addition, the manufacturer must enter the requested information in the ePQS platform and submit to WHO the relevant product dossier. Once the product dossier has been received by WHO, it undergoes screening for completeness.

Under this proposed revised process, the full prequalification assessment includes the following three components:

- review of a full product dossier;
- manufacturing site(s) inspection; and
- labelling review;

while an abridged prequalification assessment includes the following three components:

- review of an abridged product dossier;
- manufacturing site(s) inspection; and
- labelling review.

Only if and when the product dossier is complete (as determined by WHO), the three main components of the prequalification assessment (namely the product dossier review, the manufacturing site inspection and the labelling review) are performed by WHO. The product dossier assessment, manufacturing site inspection and labelling review are implemented concurrently.

Once the aforementioned three components are completed, WHO makes a decision (taking into account the outcomes of the performance evaluation pre-requisite and of the aforementioned three assessment components) on whether or not to prequalify the product in question.

If WHO determines that the product in question meets all WHO acceptance criteria and requirements in respect of the performance evaluation and each of the three prequalification assessment components, the product will be prequalified and included in WHO's list of prequalified IVDs provided however that, among other things, that the manufacturer timely fulfill all post-prequalification commitments.

If the product in question does not meet all WHO acceptance criteria and requirements in respect of the performance evaluation and each of the three prequalification assessment components, then the product will not be prequalified and the application will be terminated.

7. Input on the proposed revisions to the WHO Prequalification of in vitro diagnostics assessment process : Public consultation

WHO is inviting stakeholders to provide input on the proposed revisions to the WHO prequalification of IVDs assessment process, as described above. In order to do so, please use the ***Template for comments*** provided with this document and send your comments by email to ***diagnostics@who.int***

The deadline for providing input is **30 November 2024**.

Please note that WHO will not be in a position to consider any comments that are submitted: (a) in any format other than the Excel sheet referred to above; (b) to any address other than the email address provided above; and/or (c) at any time after the abovementioned deadline.