ABRIDGED PREQUALIFICATION ASSESSMENT

Prequalification of In Vitro Diagnostics

DRAFT FOR COMMENT

comments to be submitted to diagnostics@who.int by 29 February 2020
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1. Introduction

World Health Organization (WHO) prequalification of in vitro diagnostics (IVDs) is coordinated through the department of Regulation and Prequalification. Focus is placed on IVDs for priority diseases and their suitability for use in resource-limited settings.

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

The abridged prequalification assessment includes the following components:

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

This document should be read in conjunction with the “Overview of the WHO prequalification of in vitro diagnostics assessment” document PQDx_007, as well as with the other relevant documents set forth in Section 7 below.

2. Intended Audience

This document has been prepared to provide manufacturers with information on the abridged prequalification assessment. Manufacturers wishing to apply for WHO prequalification of their product(s) should read this document before submitting the pre-submission form for prequalification.

3. Definitions

Abridged WHO prequalification assessment
Prequalification assessment by WHO including review of an abridged product dossier, performance evaluation, manufacturing site inspection of abridged scope and labelling review

4. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLA</td>
<td>Biologics License Application</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>GHTF</td>
<td>Global Harmonization Task Force</td>
</tr>
<tr>
<td>HSA</td>
<td>Health Sciences Authority of Singapore</td>
</tr>
<tr>
<td>IFU</td>
<td>Instructions for use</td>
</tr>
<tr>
<td>IMDRF</td>
<td>International Medical Device Regulators Forum</td>
</tr>
<tr>
<td>IVD</td>
<td>In vitro diagnostic medical device</td>
</tr>
<tr>
<td>JMHLW</td>
<td>Japanese Ministry of Health, Labour and Welfare</td>
</tr>
<tr>
<td>PMA</td>
<td>Premarket Approval</td>
</tr>
<tr>
<td>TGA</td>
<td>Australian Therapeutic Goods Administration</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
5. Rationale for abridged assessment

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

The aim of an abridged prequalification assessment is to avoid duplication of effort and reduce the time taken to prequalify a product by focusing on aspects where WHO prequalification assessment brings added value. WHO will review the pre-submission form and supporting documentation to determine whether the product qualifies for an abridged prequalification assessment. Products that do not qualify for abridged prequalification assessment will undergo a full prequalification assessment.

WHO will apply the abridged prequalification assessment process, in accordance with this document, 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.

WHO reserves the right to shift from an abridged assessment to a full assessment at any stage in the prequalification assessment process, if the manufacturer fails to submit satisfactory evidence supporting a previous stringent review.

6. Abridged assessment process

6.1. Eligibility for abridged assessment

When considering whether a product qualifies for an abridged assessment procedure, WHO takes into account two factors: whether the product has been stringently assessed and, if so, whether the regulatory version of the product submitted for prequalification is the same regulatory version that was stringently assessed. The assessments by the following regulatory authorities for the following risk classes are considered to be stringent for purposes of WHO’s abridged prequalification assessment, see Table 1.

Table 1 - Recognized stringent assessment

<table>
<thead>
<tr>
<th>Regulatory authority</th>
<th>Risk classes undergoing stringent assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union</td>
<td>Annex II, List A (IVDD), Class C and Class D (IVDR)</td>
</tr>
<tr>
<td>Food and Drug Administration of the United States of America</td>
<td>Class III</td>
</tr>
<tr>
<td>Health Canada</td>
<td>Class III and Class IV</td>
</tr>
<tr>
<td>Therapeutic Goods Administration, Australia</td>
<td>Class 3 and Class 4</td>
</tr>
<tr>
<td>Ministry of Health, Labour and Welfare, Japan</td>
<td>Class III</td>
</tr>
<tr>
<td>Singapore Health Sciences Authority</td>
<td>Class C and Class D</td>
</tr>
</tbody>
</table>

1 The “same 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 differs in any way between the submissions to different regulatory authorities or assessment bodies (United States Food and Drug Administration, Health Canada, a Notified Body for CE marking, etc.) it is considered to be a different regulatory version.
Based on these factors, a product is eligible for abridged assessment if one of the following conditions is met:

- The regulatory version submitted for WHO prequalification has undergone prior recognized stringent assessment by one of the regulatory authorities listed in Table 1 of this document (hereinafter referred to as a “Recognized SRA”); or
- The regulatory version submitted for WHO prequalification is different from the version that underwent regulatory review by a Recognized SRA, but there are no substantial differences between the two regulatory versions that will have impact on the safety, quality or performance of the IVD.

Conversely, a product is not eligible for abridged assessment if:

- The regulatory version submitted for WHO prequalification is different from the version that underwent regulatory review by a Recognized SRA, and there are substantial differences between the two regulatory versions; or
- No stringently assessed regulatory version of the product exists. This includes products previously assessed by a Recognized SRA, but not according to an appropriate level of stringency (lower risk classification), and products previously assessed by a regulatory authority other than a Recognized SRA listed in Table 1.

Products which are determined by WHO to not be eligible for abridged prequalification assessment will be required to undergo a full prequalification assessment.

Figure 1 summarizes the eligibility requirements and decision process for abridged assessment.

**Figure 1- Decision tree for abridged assessment**

Was the product stringently assessed and approved by a Recognized SRA

- **YES**
  - Is the regulatory version submitted for prequalification the same as that assessed by the Recognized SRA
    - **YES**
      - Are there substantial differences between regulatory versions?
        - **NO**
          - Abridged prequalification assessment
        - **YES**
          - Full prequalification assessment
    - **NO**
      - Full prequalification assessment

- **NO**
  - Full prequalification assessment
Differences between a full and an abridged prequalification assessment

The full prequalification assessment process includes the following components:
• review of a full product dossier;
• performance evaluation, including operational characteristics;
• inspection of a manufacturing site of full scope; and
• labelling review.

An abridged assessment considers available evidence that an eligible product meets certain WHO prequalification requirements as a result of its stringent regulatory approvals. Table 2 lists the differences between a full and an abridged prequalification assessment. Additional details are provided in Section 6.2 below.

### Table 2 - Differences between a full and an abridged prequalification assessment

<table>
<thead>
<tr>
<th>PQ stage</th>
<th>Full assessment</th>
<th>Abridged assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of a product dossier</td>
<td>Full product dossier</td>
<td>Abridged product dossier</td>
</tr>
<tr>
<td>Inspection of a manufacturing site</td>
<td>Inspection of manufacturing site(s) of full scope</td>
<td>Manufacturing site inspection of abridged scope</td>
</tr>
<tr>
<td>Performance evaluation, including operational characteristics</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Labelling review</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

6.2. **Abridged assessment process**

**Pre-submission stage**

A prequalification pre-submission form must be submitted by the manufacturer to WHO. Such form will serve to:
• provide information on the product submitted for prequalification;
• identify the regulatory version submitted for prequalification; and
• determine the differences between existing regulatory versions of the product.

WHO will determine (i) if there is acceptable evidence of prior stringent assessment and approval for the product submitted for prequalification, and (ii) if the product is eligible for abridged assessment. For such evidence to be considered acceptable, the product must meet the requirements for placing on the market in the respective regulatory jurisdiction. Table 3 and 4 show acceptable evidence for abridged prequalification assessment.

### Table 3 - Acceptable evidence of stringent regulatory assessment for GHTF/IMDRF Class D IVDs

<table>
<thead>
<tr>
<th>Recognized SRA</th>
<th>Acceptable evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union</td>
<td>EC Full Quality Assurance Certificate and EC Design Examination Certificate,</td>
</tr>
<tr>
<td></td>
<td>EC Production Quality Assurance Certificate and EC Type-Examination Certificate.</td>
</tr>
<tr>
<td>Recognized SRA</td>
<td>Acceptable evidence</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>European Union</td>
<td>EC Full Quality Assurance Certificate</td>
</tr>
<tr>
<td></td>
<td>EC Production Quality Assurance Certificate</td>
</tr>
<tr>
<td></td>
<td>EC Type-Examination Certificate</td>
</tr>
<tr>
<td></td>
<td>Certificate under Annex IX of the IVDR</td>
</tr>
<tr>
<td></td>
<td>Certificates under Annex X and XI of the IVDR</td>
</tr>
<tr>
<td>Food and Drug Administration of the United States of America</td>
<td>PMA letter or BLA license</td>
</tr>
<tr>
<td>Health Canada</td>
<td>Medical Device License</td>
</tr>
<tr>
<td>Therapeutic Goods Administration, Australia</td>
<td>TGA Full Quality Assurance Certificate; or</td>
</tr>
<tr>
<td></td>
<td>TGA Production Quality Assurance Certificate and Type-Examination Certificate</td>
</tr>
<tr>
<td>Japan Ministry of Health, Labour and Welfare</td>
<td>JMHLW Minister’s Approval</td>
</tr>
<tr>
<td></td>
<td>Registration to JMHLW of Manufacturer (seizogyo touroku)</td>
</tr>
<tr>
<td></td>
<td>Registration to JMHLW of Foreign Manufacturer (gaikoku seizogyosha touroku)</td>
</tr>
<tr>
<td>Singapore Health Sciences Authority</td>
<td>Listing on the Singapore Medical Device Register (SMDR) as</td>
</tr>
<tr>
<td></td>
<td>Class D IVD.</td>
</tr>
</tbody>
</table>

Table 4 - Acceptable evidence of stringent regulatory assessment for GHTF/IMDRF Class C IVDs

6.2.1. **Decision to abridge prequalification assessment**

WHO will determine if the product qualifies for abridged assessment according to Section 6.1 above. If the regulatory version submitted for WHO prequalification is different from the version that underwent regulatory review by a Recognized SRA listed in Table 1, WHO will compare the

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2 Based on the full review by HSA.
key differences between the stringent regulatory version and the regulatory version submitted for prequalification. These differences may include the product description, intended use, test procedure, labelling and instructions for use, quality management system, design, manufacturing site, key suppliers, verification/validation studies, and lot release criteria.

As described in Section 6.1 above, if there are substantial differences, the full prequalification assessment will be performed. If there are no substantial differences, the abridged prequalification assessment will be performed.

NOTE: In some cases, a product may have multiple regulatory versions and associated approvals and more than one of the different types of evidence specified in Tables 3 and 4. Each of these approvals may support different aspects of the WHO requirements, further facilitating the abridged prequalification assessment. Therefore, it is important for the manufacturer to submit to WHO all available evidence of previous stringent regulatory approvals.

6.2.2. Abridged product dossier review

If the product qualifies for abridged prequalification assessment, the manufacturer must submit the abridged product dossier according to the requirements and provisions set forth in the Product Dossier Checklist.

6.2.3. Manufacturing site(s) inspection of abridged scope

Under the abridged prequalification assessment, a manufacturing site inspection of abridged scope will take place. The on-site inspection will be limited to those product- and user-specific processes that are a major focus of WHO prequalification inspections (e.g. risk management, in-use stability under poorly controlled conditions, impact on stability of transportation, information gathered from the market etc., user training and training material additional to the IFU, etc.).

In addition to the above-referenced processes, the abridged inspection scope will also take into consideration the findings of the most recent regulatory audit report. There will be limited sampling of some of the general quality management processes and associated records and a follow-up on, or clarification of, individual findings identified in the available report.

A preliminary report (i.e., close out record) detailing issues of concern (if any) will be provided to the manufacturer usually—but not necessarily—on the final day of the inspection. A final inspection report, including the graded nonconformities will be issued to the manufacturer after the inspection of the manufacturing site(s) as per relevant WHO timelines.

All nonconformities, regardless of their grading, must be actioned by the manufacturer, as part of a corrective action plan (or CAPA), through suitable corrective actions that identify and address the root cause of each nonconformity. The manufacturer will have the opportunity to submit to WHO up to two corrective action plans. Depending on the nature and number of nonconformities, objective evidence of the effective implementation of proposed corrective actions may be required to be provided by the manufacturer to WHO. WHO will assess the information and evidence provided and decide whether the corrective action plan can be accepted. Conformity with WHO’s prequalification requirements will be established based on, among other things, the Organization’s assessment of such information and evidence. The number and criticality of

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1 For further information refer to Annex 1: Abridged product dossier requirements

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nonconformities may require that the effective implementation of proposed corrective actions be verified by WHO in a follow up inspection, before the nonconformities may be closed off.

If the product successfully meets WHO’s prequalification requirements, a summary of the findings of the inspection of the manufacturing site(s) will be included in the WHO prequalification public report. In certain cases, WHO may, in its sole discretion, permit the manufacturer to correct specific nonconformities after prequalification, provided that the manufacturer commits in writing to address them by an agreed upon deadline. Such a “commitment to prequalification” will be reflected in the WHO prequalification Final Report Letter and will be verified during any follow-up inspection. Failure by the manufacturer to comply with its commitments to prequalification within the agreed deadlines will result in the removal of the product from WHO’s list of prequalified IVDs.

6.2.4. Performance evaluation

The purpose of the performance evaluation is to independently verify and evaluate the performance and operational characteristics of the product. It is carried out by specified WHO Collaborating Centre(s) or designated laboratory(ies) (collectively referred to as “evaluating site(s)”), using the WHO prequalification evaluation protocol. The product will be evaluated against pre-determined performance criteria established by WHO.

The manufacturer must choose one of the following two performance evaluation options, and must indicate its choice in the pre-submission form:

- Option 1: Performance evaluation commissioned by WHO and carried out at an evaluating site listed by WHO. The manufacturer must indicate in the pre-submission form its choice to undergo a performance evaluation coordinated by WHO and performed by an evaluating site selected by WHO.

- Option 2: Performance evaluation commissioned by the manufacturer and carried out at an evaluating site listed by WHO. The manufacturer must indicate in the pre-submission form its choice to have the performance evaluation performed by an independent laboratory selected by the manufacturer from the list of prequalification evaluating sites. If this option is chosen, the manufacturer will be responsible for paying the full cost of the performance evaluation (in addition to paying the applicable prequalification assessment fee) and for coordinating the performance evaluation directly with the evaluating site.

Regardless of the option chosen, the performance evaluation must be carried out in accordance with a publicly available WHO protocol developed in collaboration with international experts. WHO will have absolute, exclusive, unfettered control over the manner in which the prequalification assessment process is carried out (including the performance evaluation and/or the publication of results of the prequalification assessment, regardless of the outcome). A summary of the performance evaluation report/findings will be included in the WHO prequalification public report, if the product successfully meets the WHO prequalification requirements.

Irrespective of whether the product meets WHO prequalification requirements, a summary of the performance 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. If the product fails to meet WHO prequalification acceptance criteria for performance evaluations, the application will be cancelled.

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4 The List of WHO prequalification evaluating laboratories is available at:
http://www.who.int/diagnostics_laboratory/evaluations/170308_list_of_pq_laboratories.pdf?ua=1
6.2.5. Labelling review

The IFU version for the product which is submitted with the pre-submission form will be considered during the abridged assessment. The manufacturer must obtain WHO’s written agreement prior to implementing any changes to this version of the IFU, otherwise, the application may be cancelled.

The product labelling will be reviewed as part of the pre-submission form, product dossier, performance evaluation and inspection of manufacturing site(s). The IFU is reviewed for clarity, correctness, consistency with the information submitted in the technical documentation and with international guidance and requirements, and suitability for the target user group in WHO Member States. The overall feedback on the labelling review will be provided to the manufacturer after all abridged assessment components have been completed. If requested by WHO, the manufacturer must amend the labelling before the product can be prequalified.

The agreed product labelling will be included in the prequalification public report.

6.2.6. Prequalification decision

WHO will determine whether the product meets the WHO prequalification requirements and can be included in the WHO list of prequalified IVDs. The decision to include the product in 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 outcomes of the product dossier review, manufacturing site(s) inspection, the performance evaluation findings and the labelling review. This decision is subject to change on the basis of new information that may become available to WHO.

6.2.7. Cancellation of Application

If the manufacturer fails to meet WHO prequalification requirements or fails to provide any information or evidence requested by WHO within the specified time periods, or if any of the other conditions outlined Section 10.3 (Cancellation of Application) of the document “Overview of the WHO prequalification of in vitro diagnostics assessment” document PQDx_007, WHO reserves the right to cancel the manufacturer’s application for prequalification of its product.

7. Relevant documents

This document must be read and understood in conjunction with other relevant documents of the WHO Prequalification of IVDs Programme including, without limitation, the following:

- Overview of the prequalification of in vitro diagnostics assessment: Document PQDx_007
- Instructions for Completion of the Pre-submission Form: Document PQDx_017
- Pre-Submission Form: Document PQDx_015
- Product Dossier Checklist: Document PQDx_049
- Instructions for Compilation of a Product Dossier: Document PQDx_018
- Information for manufacturers on the manufacturing site(s) inspection (assessment of the quality management system) Geneva: World Health Organization PQDx_014.

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5 Documents can be accessed through the WHO website: http://www.who.int/diagnostics_laboratory/evaluations/en/PQDx_173 V4 DRAFT 19 December 2019
Annex 1: Abridged product dossier: draft requirements

Abridged product dossier content requirement

1. ADMINISTRATIVE

1.1 Cover letter
1.3 List of terms
1.4 Application form
1.5 Listing of devices
1.6 QMS or other regulatory certificates
1.7 Free sale certificate / Certificate of marketing authorisation
1.8 User fees
1.11 Statements/Certifications/Declarations of conformity

2. SUBMISSION CONTEXT

2.4 Device description
2.4.1 Comprehensive device description and principle of operation
2.4.3 Description of device packaging
2.5 Indications for use and/or intended use
2.5.1 Intended use; Intended purpose; Intended user; Indications for use
2.5.2 Intended environment / setting for use
2.6 Global market history
2.6.1 Global market history
2.6.2 Global incident reports and recalls
2.6.4 Evaluation / inspection reports
2.7 Other submission context information
2.7.2 Training and support networks

3. NON-CLINICAL EVIDENCE

3.2 Risk management
3.5 Analytical performance
3.5.4.2 Precision of measurement (repeatability and reproducibility) - If applicable, studies to establish repeatability undertaken by non-laboratory personnel are provided
3.6 Other studies
3.6.4 Usability / Human factors
3.6.5 Stability of the IVD
3.6.5.1 Claimed shelf life
3.6.5.2 In-use stability
3.6.5.3 Shipping stability

5 LABELLING AND PROMOTIONAL MATERIAL

5.2 Product/package labels
5.3 Package insert/Instructions for use
5.6 Technical / operators manual
5.8 Other labelling and promotional materials
6. Information package contents:

<table>
<thead>
<tr>
<th>Element</th>
<th>Required documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Management System</td>
<td>Quality manual including staff organogram</td>
</tr>
<tr>
<td></td>
<td>List of current quality management procedures</td>
</tr>
</tbody>
</table>
| Standard operating procedures for: | }
| Complaint handling and vigilance | }
| Control of nonconforming goods/processes | }
| Change control/change notifications (product and processes) | }
| Risk management | }
| Supplier evaluation and control, verification of purchased product | }
| Design and development | }
| Audit report of the most recent full regulatory inspection/audit and all subsequent surveillance inspections/audits | }
| Any valid quality management system certificate(s) (e.g. ISO 13485) | }
| Name and contact details of the responsible person at the site of manufacture regarding the inspection | }
| Product | Labelling (instructions for use (IFU), component labels and box labels) |
|         | Photographs of kit, box including contents, kit components |
|         | Accessories (including photographs) |
|         | Copy of current product regulatory approval certificate(s) |
|         | Summary of changes initiated or applied to the product subsequent to the above regulatory approvals |
| Manufacturing | Full address, including latitude and longitude of the manufacturing facility(s) |
|         | Site floor plan |
|         | Manufacturing flowchart including in-process control points |
|         | List of critical raw materials (including details of the supplier of each material) |
|         | List of outsourced processes with direct product impact (e.g. outsourced manufacturing of components (conjugated antibodies, strips, reagents, outsourced laboratory testing, packaging, printing, etc.) including details of the supplier for each process |

The quality management system-related information referenced under the Information package will be integrated in the abridged product dossier following the ToC format.