INSTRUCTIONS FOR THE COMPLETION OF THE PREQUALIFICATION OF IN VITRO DIAGNOSTICS PRE-SUBMISSION FORM

WHO Prequalification of In Vitro Diagnostics Programme

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Scope

In order to be considered for prequalification assessment, manufacturers must complete a pre-submission form.

This document has been prepared to assist manufacturers in correctly completing the prequalification of in vitro diagnostics pre-submission form (document number PQDx_015).

It is recommended that manufacturers who wish to apply for WHO prequalification of an in vitro diagnostic read the instructions in this document and the pre-submission form before attempting to complete it.

The numbering of the sections in this document corresponds to those in the pre-submission form.

NOTE: pre-submission forms that are not completed correctly or that do not provide all requested information may not be considered for prequalification.

Submitting the pre-submission form

Manufacturers wishing to apply for WHO prequalification of their product(s) should read the Overview of the prequalification of in vitro diagnostics assessment document before completing and submitting 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 diagnostics@who.int for review.

NOTE: Manufacturers must not submit a product dossier along with the pre-submission form. Dossiers that are submitted without a formal request from WHO will be destroyed without prior notice.

1. Manufacturer Information

1.1 Legal manufacturer

For the purpose of prequalification, WHO uses the following definition of "manufacturer"[1].

"Manufacturer" means 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).
The person or company who represents themselves as the manufacturer on the product label, is considered for WHO purposes, the manufacturer for the product, even if that person or company organizes for another party to carry out manufacturing tasks on their behalf.

[1]From Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

WHO only accepts prequalification applications directly from the manufacturer as defined above.

Where a parent company exists for a manufacturer, this information should be disclosed.

NOTE: 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.

1.2. Authorized contacts for the manufacturer

The "authorized contacts for the manufacturer" are two people explicitly designated by the manufacturer to represent that manufacturer for the purposes of the WHO prequalification.

NOTE: These two authorized representatives will be the primary contact points for WHO in relation to all prequalification applications submitted by the manufacturer. Therefore, please ensure that all contact details provided in the pre-submission form are current.

WHO suggests that the manufacturer ensures that the product manager/marketing and the technical/manufacturing functions of the manufacturer are covered by the two selected authorized contacts.

A signed letter from the manufacturer stating that these two people are authorized to represent the manufacturer for the purposes of prequalification must be attached to the pre-submission form.

The manufacturer should notify any changes to the authorized contacts to WHO.

2. Product – Information

2.1. Product name and product code/catalogue number for WHO prequalification assessment[2]

2.1.1. Only one in vitro diagnostic is permitted per pre-submission form. Provide the name for one product only.

2.1.2. Provide the product code/catalogue number and the product kit size here. If the product is available in multiple kit sizes, provide this information for each individual product kit size.

2.1.3. If reagents are provided in multiple boxes, provide the name and product code/catalogue number for each size of reagent box. For example, if controls are provided separately to the test reagents, provide the catalogue number for the controls here. In addition, the number of tests for each box of reagents should be provided.

2.1.4. A "**dedicated instrumentation**" defines a situation where the assay must be run on a specific instrument as part of the testing protocol. The instrument and assay reagents are only

[2] WHO must be notified of all changes made to this product, as per document PQDx_007 Overview of the prequalification of in vitro diagnostics assessment.

ever used in combination to perform the assay. If dedicated instrumentation is required to perform the assay please provide the name of the instrument(s) or component(s) and possible combinations of these as well as the relevant product code(s)/catalogue number(s) (e.g. for the nucleic acid extraction units, amplification units, etc.).

2.1.5. A "**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.

2.1.6. Please only indicate the year related to the regulatory version of the product being submitted for prequalification.

2.2. Current instructions for use and user manual

Provide document control details for the instructions for use documentation and the user manual(s) relevant to this product.

Attach to the application form a copy of the English language version of the instructions for use (package insert).

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.

2.3. Transport, storage and operating temperatures

2.3.1. The transport, storage and operating temperature ranges must be clearly specified by the manufacturer. The manufacturer's specified transport, storage and operating temperatures ranges and shelf-life period upon manufacture should be provided for the assembled product.

"Shelf-life upon manufacture" is the period of time from when the product is released for supply until the expiry date - during which the product performance is assured by the manufacturer.

For products where reagents are provided in more than one box, provide the transport, storage and operating temperature ranges and shelf-life periods for each box of test reagents required to perform the assay.

2.3.2. If there are any other specified storage conditions applicable to this product, also provide details of these storage requirements.

NOTE: If this product is accepted for prequalification assessment, you will be required to provide evidence as part of your product dossier submission (such as data generated through stability studies) demonstrating that the product continues to perform within specifications, to support all claims.

3. Product – Disease Category, Analyte and Method

For questions 3.1 - 3.8. tick/check the boxes that are relevant to your product.

Section 3.7 applies only to CD4 technologies and should be left blank for other types of products.

4. Product – Operation

4.1. Assay controls

A "**specimen addition control**" provides confirmation to the user of the assay that the specimen being tested has been added to the assay.

"**Control samples**" (also called "test-kit controls") refer to preparations that are specifically designed by the manufacturer for this particular assay. These control samples are usually a positive and a negative control specimen.

4.2. Product usage

"**Single run**" refers to the number of specimens that can be tested consecutively by one operator without interruption (unless the recommended operation requires such interruption).

4.3. Indicative cost

Please provide the indicative cost per test in US Dollars and if applicable, the cost of the dedicated instrumentation required to perform the assay.

5. Product – Performance Characteristics

5.1. Performance characteristics for serology

"**Sensitivity**" refers to clinical or diagnostic sensitivity. "Sensitivity" is the ability of a test to give a positive result for individuals that have the disease or disorder for which they are being tested. The disease status of the individual must be predefined by criteria that are independent of the test under consideration.[3]

"**Specificity**" refers to clinical or diagnostic specificity. "Specificity" is the ability of a test to give a negative result for individuals that do not have the disease or disorder for which they are being tested. The negative disease status of the individual must be predefined by criteria that are independent of the test under consideration.[3]

5.2. Specifications for CD4 Technologies

Section 5.2. applies only to CD4 Technologies and should be left blank for other types of products.

5.3. Specifications for Virological Technologies

Section 5.3. applies only to Virological Technologies and should be left blank for other types of products.

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[3] This definition is based on terminology used in the publicly available "Harmonized Terminology Database" that is compiled by the Clinical and Laboratory Standards Institute. See www.clsi.org

5.4. Independent performance evaluations

An "**independent performance evaluation**" is a performance evaluation of the product that has been carried out by an impartial centre of excellence that has no professional or personal interests in the manufacturer or the product.

NOTE: The manufacturer should ensure that any independent performance evaluations are carried out by centres that have the capability of performing scientifically sound evaluation studies for the product in question.

6. Regulatory and Commercial status of the Product

6.1. Regulatory status of the product

6.1.1. Please refer to the definition of regulatory version provided in section 3.1.5. and identify the regulatory version of the product submitted for prequalification.

6.1.2. Please tick/check the boxes that are relevant to your product and provide details of all current regulatory approvals for this product.

"National Regulatory Authority" means a government body or other entity that exercises a legal right to control the use or sale of in vitro diagnostics within its jurisdiction, and may take enforcement action to ensure that in vitro diagnostics marketed within its jurisdiction comply with legal requirements.

"**Regulatory Approval**" means that the National Regulatory Authority officially permits supply of this in vitro diagnostic product in the country/region under its authority.

"**Type of Regulatory Approval**" refers to the relevant sections of the legislation that have been applied to the product for regulatory approval. Generally the details of the legislation applied for regulatory approval should be included on the certificate that demonstrates that the product is approved for supply.

NOTE: Do not include certification information relating to ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes here. Questions relating to ISO 13485:2003 are addressed in Section 8 of the pre-submission form.

6.2. Commercial agreements and re-branding

WHO requires this commercial agreement information available in order to determine which in vitro diagnostic products are of priority for prequalification.

6.3. WHO history of product

Provide information on previous WHO assessment of the product.

7. Manufacturer – Quality Management System

An effective quality management system is a key consideration for all manufacturers of in vitro diagnostics. Therefore, products submitted for prequalification assessment must be manufactured under an appropriate quality management system.

The quality management standard ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes is considered to be a benchmark in quality management for the manufacturers of diagnostic products by regulatory agencies throughout the world. WHO bases its in vitro diagnostics prequalification assessment and inspection processes on the requirements of this internationally recognized quality management standard.

Provide information about the manufacturer's quality management system and conformity to the referenced standards.

8. Manufacturer – Quality Management System Certification

If the manufacturer holds "ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes" certification for the manufacture of this product, then provide details of this certification here. This certification must cover the manufacturer taking responsibility for the product, and all sites involved in the manufacture of the product.

NOTE: The manufacturer will be required to provide evidence of all quality management system claims as part of the product dossier submission.

9.2. Production

Provide information on the number of lots manufactured per year, their average size and the total number of products manufactured per year (including instruments).

9. Manufacturer – Sites of Product Manufacture

9.1. Sites of manufacture

List all sites that are involved in the manufacture of this product. Include all stages of manufacture, for example design and development, assembly, labelling, packaging, lot release quality control, release for supply etc.

9.2. Key suppliers

List all key suppliers which supply products/components/services for the manufacture of this product

10. Manufacturer Declaration

This declaration must be completed before WHO will consider the product for prequalification assessment. The declaration must be duly signed by the key authorized contact for the manufacturer designated under section 2.2.

Annex 1: Review of differences to establish eligibility for abbreviated prequalification assessment

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, WHO will review the differences between the two regulatory versions to determine eligibility for abbreviated assessment, based on the information provided in Annex 1.

Provide information on the product, its design and manufacturing and labelling.

11. Relevant Documents

WHO Prequalification of IVDs Programme[4]

- Overview of the prequalification of in vitro diagnostics assessment: Document PQDx_007
- Pre-Submission Form: Document PQDx_015
- Abbreviated prequalification assessment: Document PQDx_173

GHTF guidance documents[5]

- GHTF/SC/N4:2011 Definition and Glossary of Terms Used in GHTF Documents
- GHTF/SG1/N68:2012 Essential Principles of Safety and Performance of Medical Devices

ISO standards[6]

- ISO 13485:2003 Medical devices - Quality management systems - Requirements for regulatory purposes [International Organization for Standardization (ISO) document

[4] Documents can be accessed through the WHO website: http://www.who.int/diagnostics_laboratory/evaluations/en/
[5] Documents can be accessed through the IMDRF website http://www.imdrf.org/documents/documents.asp
[6] Documents can be purchased through the International Organization for Standardization website http://www.iso.org/iso/home.html