



# **INSTRUCTIONS FOR THE COMPLETION OF THE PRE-SUBMISSION FORM**

*Prequalification of In Vitro Diagnostics*

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## I. Introduction

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.

Manufacturers applying for WHO prequalification assessment of IVDs are required to complete the form PQDx\_015 *“Pre-submission form”*. The pre-submission form assists WHO to determine eligibility for prequalification assessment and the type of assessment (full or abridged) that the product will undergo. This document is intended to assist manufacturers in correctly completing the pre-submission form.

## II. Intended audience

Manufacturers who wish to apply for prequalification assessment of their product(s) should read the instructions in this document and the pre-submission form before attempting to complete the pre-submission form. In addition, manufacturers should read the document PQDx\_007 *“Overview of the WHO Prequalification of In Vitro Diagnostics assessment”* before applying, so that they can be aware of and prepared for all stages of the prequalification assessment process.

## III. Submitting the pre-submission form

The pre-submission form and the respective attachments (authorization letter, photographs, instructions for use and abridged assessment eligibility annex) is required to be submitted electronically to [diagnostics@who.int](mailto:diagnostics@who.int). It is requested that all documents are submitted as searchable PDF files.

Manufacturers will be provided with two opportunities to correctly complete the pre-submission forms will all requested information. If the manufacturer fails to provide the information after two attempts, the application will be rejected.

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.

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

### 1. Manufacturer Information

#### 1.1. Legal manufacturer

For the purpose of prequalification, WHO uses the following definition of "manufacturer"<sup>1</sup>.

**“Manufacturer”** means any natural or legal person with responsibility for design and/or manufacture of an IVD with the intention of making the IVD available for use, under his or her name, whether or not such an IVD is designed and/or manufactured by that person him- or herself or on his or her behalf by (an)other person(s).

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<sup>1</sup>From Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2) available at <http://www.imdrf.org/docs/ghtf/final/steering-committee/procedural-docs/ghtf-sc-n4-2012-definitions-of-terms-121109.pdf>

Applications for WHO prequalification of IVDs are accepted only from the legal manufacturer of the product.

## 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.

These two authorized representatives will be the primary contact points for WHO in relation to the prequalification application submitted by the manufacturer. Therefore, the manufacturer is requested to 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<sup>2</sup>

2.1.1. Only one IVD 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.

- For products available in multiple kit sizes: list the kit size and product code for each individual kit size.
- For products with multiple kit configurations: list the contents, the quantity or volume of each component and product code (if applicable).
- Photographs of all kit components (packaged and individually) must be attached to the pre-submission form.

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.

- For each different box size of reagent, list the number of tests and product code for each box size

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 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.).

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<sup>2</sup> 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*.

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.

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

NOTE: Applications for WHO prequalification of IVDs are only accepted for products that are commercially available at the time of submission for prequalification assessment. Any exemptions must be agreed upon by WHO prior to the submission of the application 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 pre-submission 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 assessment, 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 in section 3, tick/check the boxes that are relevant to your product.

### 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 EIAs and RDTs

"**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.<sup>3</sup>

"**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.<sup>3</sup>

#### 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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<sup>3</sup> 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](http://www.clsi.org)

## 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 2.1.5. 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 Medical devices — Quality management systems — Requirements for regulatory purposes here. Questions relating to ISO 13485 are addressed in Section 7 of the pre-submission form.

### 6.2. Commercial agreements and re-branding

WHO requires this commercial agreement information available in order to determine eligibility for prequalification assessment. Applications for WHO prequalification of IVDs are accepted only from the legal manufacturer of the product.

### 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 IVDs. Therefore, products submitted for prequalification assessment must be manufactured under an appropriate quality management system.

The quality management standard *“ISO 13485 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 prequalification assessment and inspection processes are based 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 certification for the manufacture of this product, then provide details of this certification in this section. This certification must list 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. Manufacturer – Sites of Product Manufacture

### 9.1. Sites of manufacture

List all sites that are involved in each and every step of the manufacture of this product. Include all stages of manufacture, as per the table provided. Please, do not modify the description of the table.

### 9.2. Contact person(s) for inspection

Should WHO determine that an inspection of the manufacturing site(s) is required, Inspection Services will need to coordinate the inspection with the relevant representative(s) of the manufacturing sites. Please provide below the details of the authorized contact(s) to allow for inspection planning. If there are multiple manufacturing sites, you may provide one contact per site.

### 9.3. 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).

### 9.4. Key suppliers

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

## 10. Performance evaluation pathway

The performance evaluation of the product is carried out by specified WHO collaborating centre(s)<sup>4</sup> or a designated laboratory or laboratories (collectively referred to as “evaluating site(s)<sup>5</sup>”), using the WHO prequalification evaluation protocol.

The manufacturer can choose one of two performance evaluation options:

- Option 1: Performance evaluation commissioned by WHO and carried out at an evaluating site listed by WHO.

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<sup>4</sup> WHO collaborating centres are institutions designated by the WHO Director-General to form part of an international collaborative network carrying out activities in support of WHO's programmes at all levels. In certain instances, additional laboratories may be contracted by WHO to perform laboratory evaluation.

<sup>5</sup> 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](http://www.who.int/diagnostics_laboratory/evaluations/170308_list_of_pq_laboratories.pdf?ua=1)

- Option 2: Performance evaluation commissioned by the manufacturer and carried out at an evaluating site listed by WHO.

The manufacturer must tick/check the box to indicate whether they choose Option 1 (undergo a performance evaluation coordinated by WHO and performed by an evaluating site selected by WHO) or Option 2 (to conduct the independent performance evaluation at a laboratory selected by the manufacturer from the list of prequalification evaluating sites). The manufacturer will bear the cost of the evaluation and be responsible for coordinating the evaluation directly with the evaluating site if they tick/check Option 2.

## **11. Manufacturer Declaration**

This declaration must be completed before the application will be considered for prequalification assessment. The declaration must be duly signed by the key authorized contact for the manufacturer designated under section 1.2.

## **Annex 1: Eligibility for abridged 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.

## **12. Relevant Documents**

The following documents provide information to guide the manufacturer through the application process for WHO prequalification of IVDs<sup>6</sup>:

- Pre-submission form. Geneva: World Health Organization (PQDx\_015).
- Overview of the WHO Prequalification of In Vitro Diagnostics assessment. Geneva: World Health Organization (PQDx\_007).
- Eligibility criteria for WHO prequalification of in vitro diagnostics assessment. Geneva: World Health Organization; (PQDx\_298).
- Abridged prequalification assessment. Geneva: World Health Organization (PQDx\_173).
- Prequalification of in vitro diagnostics assessment and change assessment target deadlines. Geneva: World Health Organization (PQDx\_300).
- WHO prequalification of in vitro diagnostics assessment and changes fees. Geneva: World Health Organization (PQDx\_299).

ISO standards

- ISO 13485 Medical devices - Quality management systems - Requirements for regulatory purposes Geneva: International Organization for Standardization (ISO).

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<sup>6</sup> Documents can be accessed through the WHO website: <https://extranet.who.int/pqweb/vitro-diagnostic/prequalification-guidance>