Instructions for compilation of a product dossier

WHO's prequalification of in vitro diagnostics

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Contents

A. Introduction

This document provides instructions to manufacturers on the type of information and necessary documents that are to be submitted in a product dossier for the purposes of WHO's prequalification assessment of in vitro diagnostic (IVD) medical devices (hereinafter "the prequalification process"). This document supersedes "*Instructions for compilation of a product dossier: prequalification of in vitro diagnostics programme"* published in 2023.

The prequalification process allows for flexibility in a manufacturer's approach to compiling the information required for an application. Alternative approaches to both the principles, and application, of the requirements described in this document may be acceptable provided they are supported by adequate scientific justification. It is recommended that manufacturers discuss in advance with the Prequalification Unit – Assessment WHO prequalification of Medical Devices team any questions about alternative approaches, so as to understand the potential impact on meeting WHO prequalification requirements.

WHO may request, during the course of the prequalification process, additional information that is not specifically described in this document. This will be done in order to facilitate a clearer understanding of the safety, efficacy and performance of a product under assessment. The rationale for any additional requests will be clearly documented in correspondence to the manufacturer.
This document is intended to be read in conjunction with the WHO document PQDx_049 *Product Dossier Checklist* and, where available the corresponding WHO Technical Specification Series document(s) (TSS) relevant to the product for which an application to prequalification is made (see section C.4 Applicability of supporting evidence to the product under review). Manufacturers wishing to submit a product dossier for an IVD are recommended to read these documents carefully to compile a successful product dossier.

Manufacturers are also recommended to refer to the WHO document PQDx_007 *Overview of WHO's prequalification procedure for in vitro diagnostics*, for a description of the steps of the prequalification process that is required to be first undertaken before submitting a product dossier.

For the purpose of this document, the verbal forms used follow the usage described below:

- "shall" indicates that the manufacturer is required to comply with the instructions in the document below
- "should" indicates that the manufacturer is recommended to comply with the instructions, but it is not a requirement.
- "may" indicates that the instructions are a suggested method to compile the documentation request, but it is not a requirement.

B. Intended audience

This document has been prepared as guidance to manufacturers of IVDs to assist in correctly compiling a product dossier for the prequalification process.

C. The product dossier

C.1 About the product dossier

There are many terms used internationally to describe a product dossier. These terms include: *standard technical documentation*, *technical file, summary technical documentation, product summary file, product master file* and others. For the purposes of prequalification of IVDs, WHO uses the term the *product dossier*.

WHO expects a manufacturer to prepare and either hold, or provide timely access to, technical documentation that shows how its IVD is designed, developed, validated, and manufactured. This technical documentation, typically controlled in the manufacturer's quality management system (QMS), is often extensive and the documentation is revised over time to reflect any changes made during the life cycle of the IVD through normal application of the manufacturer's QMS.

The product dossier is a selection of records and documents from the entire collection of technical records and documents that a manufacturer holds for a product. Manufacturers compile a product dossier from their existing technical documentation to provide evidence that an IVD conforms to the internationally-recognized set of quality, safety and performance principles as described in the International Medical Device Regulators Forum (IMDRF) document IMDRF/GRRP WG/N47 FINAL[1] *Essential Principles of safety and performance of medical devices and IVD medical devices* (hereinafter "the Essential Principles"). Evidence will take the form for example, of results of testing, certifications, standard operating procedures (SOPs), systems and any other documentation necessary to support quality, safety and performance.

WHO requires that a product dossier is submitted in the "Table of Contents" (ToC) format, described in the IMDRF document IMDRF/RPS WG/N13 FINAL[2] *"In Vitro Diagnostic Medical Device Regulatory Submission Table of Contents (IVD ToC)"*. In this document chapters 1-6 and their subheadings, as well as the corresponding chapters and subheadings of the *Product Dossier Checklist* are numbered according to IMDRF ToC format. As the IMDRF ToC is comprehensive in nature, not all subheadings are required for WHO prequalification and are excluded. As a result, the subheading numbering in the *Product Dossier Checklist* (PQDx_049) is not always continuous (e.g. 4.2, 4.5 etc). This has been done so as to maintain consistency between sections required in a product dossier for WHO prequalification assessment and the corresponding numbering defined in the IMDRF ToC format.

[1] As amended from time to time
[2] As amended from time to time

WHO reviews the product dossier with the purpose of:

- assessing the product and how it performs
- assessing the product manufacture
- determining if the manufacturer's quality management system is of an adequate standard to warrant a WHO prequalification site inspection

C.2 Submission of a product dossier

For a full prequalification assessment, WHO will formally invite a manufacturer to submit a product dossier; a product dossier should not be submitted unless one is requested. If a product is eligible for an abridged assessment the manufacturer will be notified in writing and requested to submit an abridged product dossier containing information for each section listed in Annex 1 - Abridged product dossier requirements.

Note: All information submitted in the product dossier is **CONFIDENTIAL**.

Once an assessment is complete, WHO reserves the right to destroy any dossier materials provided with the application.

C.3 Product dossier clarity and completeness

Manufacturers shall submit all necessary sections of a product dossier, identified both in this document and in the *Product Dossier Checklist* (PQDx_049). All sections listed in this document are required to be submitted as part of the product dossier unless indicated “if applicable”.

Not providing the required information may result in WHO not accepting the dossier, significant delays in the assessment process, or cancellation of the assessment process.

Manufacturers should make every effort to ensure that their product dossier is clear and well-organized. Poorly prepared dossiers are an obstacle to efficient prequalification assessment and may be rejected without full review.

Do not duplicate files, even if it is possible to include the same evidence under multiple subheadings. Provide the evidence under one appropriate subheading and then make specific references (including both section and page numbers) to that material in any subsequent sections that appear relevant. Be specific: references to specific sections or pages of a document should be provided when possible.

C.4 Applicability of supporting evidence to the product under review

The manufacturer shall carry out relevant investigations to support the intended use, such as analytical and clinical sensitivity and specificity, accuracy, repeatability, reproducibility, linearity, detection limits, and traceability, as appropriate. In addition, WHO requires investigations to assess the potential effects of interfering factors and claims of reagent and product stability. Studies in support of the intended use should consider the intended user and the intended setting of use.

WHO Technical Specifications Series (TSS) have been prepared for many of the IVDs eligible for Prequalification assessment. Each TSS sets out the

appropriate product performance evaluation criteria for specific IVDs being accepted for prequalification assessment. The TSS provides information regarding the minimum performance requirements that shall be met by a product to ensure that it is safe and performs optimally.

The analytical and clinical performance characteristics described in chapters 3 and 4 of this document may not necessarily apply to all types of products submitted for prequalification assessment. Where a corresponding TSS is available for its product type the manufacturer is recommended to refer to that TSS for clarification as to which of the studies are needed to support an application, as well as details of the requirements for these studies.

The current list of product-specific TSS documents is available at: https://extranet.who.int/prequal/vitro-diagnostics/technical-specifications-series-ivds

The manufacturer may also refer to Technical Guidance Series (TGS) document, "Principles of Performance Studies (TGS-3)" for additional detailed information.

For each performance study submitted in a product dossier, the following shall be provided:

- **Study Description:** A description of the study that includes information to facilitate record traceability: study identifier, product identifier (for example, lot numbers), IFU version used, the date of initiation and the date of completion. All data shall be clearly labelled and linked to the study report.
- **Study summary:** A summary of the study findings, including a conclusion that clarifies how the study objectives have been met.
- **Full study protocol and report**: The study protocol and full report, which incorporates at a minimum, the following information:
    - study objectives, study design, the method used and data collected
    - the site(s) where the study was performed (for example, manufacturers research and development laboratory, hospital laboratory, health care clinic)
    - operator(s) of the assay
    - the reference standard/method, if applicable
    - specimen acceptance/selection criteria, details of specimen characterisation
    - specimen type(s) (e.g. serum, plasma, finger stick whole blood, venous whole blood) and numbers of each type
    - actual test result summaries with their acceptance criteria, not just pass/fail statements
    - results that are reported in sufficient detail to allow the detection of potential differences in performance between the conditions being investigated (e.g. depending on the product this might require the use of either a semi-quantitative scoring

system or a calibrated, graduated colour chart to record line intensity)

- the numbers of invalid tests observed
- photographs of test results, wherever possible
- details of statistical methods, estimations and calculations applied
- the study conclusion
- when performed by a party other than the manufacturer, details of this third party and the relationship to the manufacturer as well as copy of the contract between the manufacturer and the third party identifying roles and responsibilities of each party.

D. Dossier format

D.1 Product dossier submission format

- Submit one electronic copy using a secure file hosting service.

D.2 Layout and order

WHO requires the following format for the dossier submission:

- Use the page numbers format page 1 of 2, 2 of 2, and so on.
- Clearly divide the submission into sections and subheadings, as prescribed in the *Product Dossier Checklist*, and number all pages of each section, including annexes, so that they are easily identified. Documentation for each section (chapter) may be submitted as separate file directories (folders). For example, the device description (Section 2.4.1 Comprehensive device description and principle of operation) may be provided in a file directory (folder) in the electronic submission that is named: “Section 2.4.1”, or similar.
- Use the *Product Dossier Checklist* as the first page, and cross-reference all sections of the dossier, including associated annexes, to this checklist.
- Ensure that there are appropriately named tab identifiers. The names shall link directly with the sections of the dossier as outlined in this document. For example, the labelling information shall be separated from the other documents by a tab identifier named “Section 5.2 Product/Package Labels”.
- The page numbers in each section of the dossier and the page numbers summarized in the *Product Dossier Checklist* should correspond.
- Font sizes for text and tables are of a style and size that are large enough to be easily legible. Fonts smaller than 11 points should be avoided whenever possible, except in tables and footnotes where a font size of 10 points is acceptable.
- Depending on the level of detail, the information requested in each section may either be:

- Provided directly in the corresponding section of the main product dossier file, preceded by an explanatory summary of the information, as appropriate, or
- Provided in summary in the corresponding section of the main product dossier file, with the detailed information (full study validation reports, photographs, other documentation, etc.) included as annexes, duly cross-referenced both in the corresponding section of the report and the *Product Dossier Checklist*.

- Refer to related annexes in the body of the text and list them in the *Product Dossier Checklist*.

D.3 Electronic copy requirements

Portable Document Format (PDF) is the primary file format used for product dossiers. However, do not include any PDF that requires a password to open it. This will result in return of dossiers to manufacturers resulting in the delay of the assessment.

Use file names that are descriptive of a file's content and meaningful to dossier reviewers. The path length for each document submitted, which includes the TOC section number (e.g. 3.6.5.1), any section sub-folder name(s), and the file name itself, **must not exceed 120 characters**. The name can have spaces, dashes (not elongated dashes), underscores, and periods. However, the name of the file shall not contain any of the following special characters as they are not compatible with WHO's storage platform:

tilde (~)
vertical bar (|)
asterisk (*)
- forward slash (/)

backward slash (\)
apostrophe (')
greater than sign (>)
quotation marks (' or ")
less than sign (<)elongated dash (–)
colon (:)
various other symbols (e.g., →,*,β,α,∞,±,™)
- hash tag (#)

backward slash (\)

- When creating a PDF from an electronic source document (e.g. Microsoft Word document) avoid using specialist application plug-ins for capture or display data; not all dossier reviewers will necessarily have access to these plug-ins.
- As far as practicable, electronic files shall contain searchable text. Electronic files made by directly scanning paper documents are generally low quality and are difficult to read; moreover, the lack of searchable text can make dossier information difficult to readily locate and may delay assessment of the dossier.
- For any scanned document, optical character recognition (OCR) should be used to allow text to be searchable. This can be verified by: (1) highlighting an area of text and (2) using the software search function to locate a particular word or phrase. If the word or phrase is not returned in the search, then the OCR did not recognize the text and it is, therefore, not searchable.

D.4 Acceptance of dossiers previously prepared for national regulatory authorities

Product dossiers should be compiled according to the WHO requirements described above. However, WHO may accept submissions previously prepared for national regulatory authorities if:

- all the information required by WHO is included
- the information is fully cross-referenced to the requirements of this document using the Product Dossier Checklist
- the information reflects current activities and practices (expired/superseded documentation shall not be used).

Manufacturers must contact WHO before submitting a product dossier to determine if a particular prior regulatory authority submission is appropriate to substitute for the dossier.

D.5 Language and units of measurement

Information in the product dossier shall be in English (unless other arrangements have been made with WHO ***before*** submission of the dossier).

Any document provided in a language other than English shall be accompanied by a certified translation that is signed and dated by the translator and where the translator has stated that it is a true and accurate translation of the original document.

All measurements units used should be expressed in the International System of Units (SI), as appropriate.

1. Regional Administrative

1.1 Cover letter

The completed letter of agreement, including an attestation demonstrating payment of fees shall be included in this section.

1.2 Submission Table of Contents

The *Product Dossier Checklist* (PQDx_049) shall be included at the beginning of the product dossier. The checklist shall be signed, dated and include a declaration attesting that all the information provided in the product dossier is current and correct.

NB: this item is a specific requirement for WHO product dossiers and does not exist as a heading in the IMDRF ToC dossier format.

1.3 List of terms/acronyms

Abbreviations used in this submission shall be defined here.

1.4 Application form/administrative information

Information that was submitted in the WHO document PQDx_15 *Pre-Submission Form* (available to download from WHO's Prequalification of IVDs website) will be considered during the review of the product dossier.

Therefore, manufacturers shall ensure that the content of the product dossier is consistent with the information submitted in the pre-submission form and that any changes in the information submitted in or as part of the pre-submission form are promptly notified in writing to WHO. This may include:

- Problems identified at the pre-submission form stage and communicated by WHO to the manufacturer and that are subsequently addressed in the product dossier submission.
- Differences in the version and/or content of the instructions for use (IFU) provided in the pre-submission form and that provided in the product dossier; the manufacturer shall document any differences between versions of the product IFU and provide a rationale for why changes took place.

A copy of the final, completed pre-submission form shall be included in this section

1.5 Listing of device(s)

In this section, the manufacturer shall summarize the different configurations/variants of the product that are intended to be the subject of the submission. This information shall be consistent with that provided in the letter of agreement. Please note, a detailed description of configurations/variants is provided in section 2.4.1.

1.6 QMS or other regulatory certificates

In this section, the manufacturer should provide evidence of a valid quality management system, such as an International Organization for Standardization (ISO) 13485[3] certificate issued by a conformity assessment body. The product under assessment shall be within the scope of the certification.

1.7 Free sale certificate/certificate of marketing authorization

In this section, the manufacturer shall provide (if applicable):

- List the national regulatory authorities that have provided current regulatory approval for the supply of this product in their country/region of authority
- Provide details of the type of regulatory approval obtained from each national regulatory authority
- Provide current evidence of the regulatory approval, such as certificates provided by the national regulatory authority.

The evidence should clearly show that the product under assessment falls within the scope of the submitted regulatory approval.

Copies must be certified by a notary public or by the manufacturer. The manufacturer may be asked to present the original copy at any time.

[3] As amended from time to time

- Information relating to export-only regulatory approvals should be clearly identifiable as export-only approvals.

1.9 User fees

The attestation of fee payment is completed and included with the letter of agreement under section 1.1 Cover letter.

1.12 Statements/certifications/declarations of conformity

1.12.5 Truthful and accurate statement

A declaration attesting that all the information provided in the product dossier is current and correct shall be signed and date and included as part of Section 1.2 Submission Table of Contents.

2. Submission context (product information)

2.4 Device description

2.4.1 Comprehensive device description and principle of operation

The dossier should include product descriptive information sufficient to allow a dossier reviewer to understand the design applied to the product and how it functions. The instructions for use (IFU) may be used to provide some of this information, on the condition that it is clearly indicated in the dossier what information can be found in the IFU. The following information shall be provided in this section:

- A general description of the principle of the assay method or principles of operation of the instrument.
- A description of the components of the assay (e.g., reagents, assay controls and calibrators), and, where appropriate, a description of the reactive ingredients of relevant components (e.g., antibodies, antigens, nucleic acid primers).
- If applicable, a description of the various configurations/variants that will be made available for the product under assessment.
- If applicable, a description of the accessories, and other products that are intended
  to be used in combination with the diagnostic (e.g. lancets, swabs, specimen transfer devices).
- Photographs of the product and all of its components including all accessories and/or auxiliary components either supplied with the product or ordered separately, as well as any variants/configurations. Photographs should comprise individual components; where possible, photographs of the entire product, in its final packaging configuration, should be provided.
- A description and photographs of the specimen collection and/or transport containers/materials that are provided with the product, or descriptions of specifications recommended for use.
- A statement as to whether the product is automated, semi-automated or manually operated.

- For automated and semi-automated assays: a description of the dedicated instrumentation, or for assays that do not require dedicated instrumentation; a description of the appropriate instrumentation characteristics; and a description of the dedicated consumables.
- A statement as to whether the test output is qualitative, semi-quantitative or quantitative.
- If applicable, a description of any software to be used with the product.

2.4.1 (g) Biological material

In this section, the manufacturer shall provide a table or list of all biological components included in the product under assessment.

- The table or list shall include (as applicable):
    - The name of the biological component (i.e. material of bacterial, viral, parasitic, animal, or human origin, such as plasma, cells, tissues, or their derivatives. For example, human CD4 cells, human plasma, recombinant proteins expressed in bacteria, monoclonal antibodies from modified murine cells, bovine or other animal material, ruminant proteins (bovine, ovine, caprine), or fish proteins).
    - Details of the use of the biological component in the product.
    - A description of steps taken for the reduction of transmission or infection risk (such as inactivation or removal of infectious or transmissible agents, certification of country of origin (e.g. to indicate transmissible spongiform encephalopathy (TSE)-free herds), validation studies or risk mitigation measures).
- Provide a determination of the residual risk of transmission or infection to the user of the device from these biological agents after risk reduction methods have been applied.
- For biological material (such as serum or plasma), include a statement indicating that the material has been tested for evidence of infection (e.g. tests for specific antigens, antibodies, nucleic acids, etc.), and the results of that testing (positive or negative for each).
    - Typically, this would include, at a minimum, testing for evidence of infection with HIV, hepatitis B virus, and hepatitis C virus by the most sensitive methods available for the given analyte.
    - If there are no such methods that apply to the product, state that this is the case.
- Provide information as to how users of the device are informed of any residual risk.

2.4.2 Material specifications

In this section, the manufacturer shall provide details of the critical raw materials used in the product.

For each of the raw materials/ingredients, provide the formulation or

composition information. For example, include information such as nucleic acid sequences for primers, ingredient lists for buffers, amino-acid sequence details for recombinant proteins, and clone and isotype of antibodies.

Depending on the intended use of the product, include a brief description of key reagents used in the test (e.g. capture antigens and/or antibodies) and how they were designed and purified (e.g. whether monoclonal antibodies were used; what epitopes are targeted).

Identify the sources of the materials from which the IVD components are constructed, which, depending on the product will include:

- Whether they are manufactured in house or purchased commercially.
- From what species they are derived.

2.4.4 History of development

In this section, the manufacturer shall provide the date of design lock down (design freeze). This is the date that final documentation is signed off, including quality control and quality assurance specifications, and the finalized method is stated in the IFU.

Where design change has occurred since the date of design lock down the manufacturer shall provide records of each such change, including:

- The reasons that each change was made.
- References to validation/verification data to support the change (this may be cross referenced to studies provided in the product dossier).
- Evidence that the product continues to comply with the Essential Principles.

Product related changes include but are not limited to product formulation, intended use, presentation, packaging, shelf life, manufacturing, quality control release criteria.

Where different versions and/or prototypes of the product are referred to in dossier, the manufacturer shall provide a table describing the version/name, with four columns (device name and/or version; description of changes from previous row; reason for the change; list of verification/validation activities (including clinical studies) conducted using this version). This table should also describe how the product IFU has changed between different versions of the product and make clear which versions of the IFU were used in different performance studies. This section shall also include an explanation, with supporting evidence as appropriate, that use of earlier versions of the product in the dossier is representative of the current product.

2.5 Indications for use and/or intended use

Relevant WHO Technical Guidance:Series: See TGS-5 Designing instructions for use for IVDs for additional detailed information regarding the content of an intended use statement.

2.5.1 Intended use; Intended Purpose; Intended User; Indications for Use

In this section, the manufacturer shall provide a description of both the intended use, and the intended user of the product. This section should provide sufficient detail to allow it to be understood:

- What the product is intended to detect (e.g. analyte).
- The function of the product (e.g., screening [e.g. for surveillance or safety of blood supply]; aiding the diagnosis and determination of a patient's disease course and prognosis; monitoring patient therapy or following their progress after treatment; staging or aid to determining the stage of a disease; disease differentiation or prediction; etc.).
- The clinical indication for the IVD (i.e. the specific disorder, condition or risk factor of interest that the product is intended to detect, define or differentiate), as appropriate.
- The type of specimen(s) required (e.g. serum, plasma, whole blood, sputum, urine, etc.) and any additives (e.g. anticoagulants used in specimen collection).
- The intended testing population (e.g. neonates, pregnant women, symptomatic individuals, etc.).
- The intended user (e.g. laboratory professional, health care worker at point-of-care, etc.).

2.5.2 Intended environment/setting for use

In this section, the manufacturer shall provide a description of the intended setting of use of the product (e.g. laboratory, point-of-care setting, etc.).

2.6 Global market history (commercial history)

2.6.1 Global market history

Different regulatory requirements apply to different international markets for IVDs. Manufacturers who market their IVDs to multiple countries often alter some aspects of their products to comply with regional regulatory requirements and marketing needs (e.g., differences in design, information within the instructions for use, different intended use statements, different batch release procedures, different sites of manufacture, different information on package labels). If such various versions of a product exist, WHO must have a clear understanding of precisely which version of the product the manufacturer is seeking to be prequalified. In this section:

- Identify if there are multiple regulatory versions of this product. If the product has multiple regulatory versions, clearly indicate which regulatory version of the product the manufacturer submitted for prequalification assessment.
- Identify the version that is being submitted for prequalification assessment. If the version has not been assessed in any jurisdiction, indicate this.

- Ensure that all documents submitted in the product dossier identify the regulatory version to which they relate. Where it is not the version submitted for prequalification assessment, a justification for its inclusion in the product dossier shall be provided. If the subject device is different in any way (e.g. design, labelling, specifications) from those approved or marketed in other jurisdictions, the differences should be described.
- Provide a list of all countries in which the product under assessment is currently supplied and the year when supply started. If the device has been marketed for greater than 10 years, a statement to this effect can be provided. This includes all countries where the device has been made available, whether in return for payment or free-of-charge, for distribution and/or use in that country.

2.6.2 Incident reports and recalls

In this section, the manufacturer shall provide:

- A list of all adverse events within the last five years that did affect, or could have potentially affected, the performance of the product, safety of the person being tested, safety of users of the product, or safety of any person associated with the product. Include details of the corrective and preventive action taken.
- Details regarding any situations in which the product was rejected by a national regulatory authority, situations in which an application for regulatory approval was withdrawn, or situations in which regulatory approval has been withdrawn. Include details of the corrective and preventive action taken.
- A list of all events within the last five years that required field safety corrective action 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).
    - Additional advice provision to customers to ensure that the product continues to function as intended.

2.6.4 Evaluation/inspection reports

In this section, the manufacturer shall provide copies of the last two evaluation/inspection reports from other parties (e.g. notified body inspection reports; medical device single audit programme [MDSAP], etc.).

2.8 Risk management

Relevant WHO Technical Guidance:Series: See TGS-7 Risk management for manufacturers of IVDs for additional detailed information.

A risk analysis shall be undertaken to identify and address all known or

foreseeable hazards related to the product, taking into account such aspects as the user(s) of the device, and the technology involved.

The information provided in this section shall contain:

- A summary report of the risks identified during the risk analysis process, including, but not limited to:
    - Risk to the patient arising from false positive or false negative results.
    - Indirect risks that may result from product-associated hazards, such as instability, which could lead to erroneous results.
    - The risk of delays in availability of results.
    - User-related hazards, such as reagents containing infectious agents.
    - Production-related risks.
    - Risks arising from the use of the product by users with minimal skills, training or experience and in the intended settings of use.
- A description of how these risks have been controlled to an acceptable level. This may be demonstrated by provision of documented evidence using risk assessment tools such as failure modes and effects analysis (FMEA), failure reporting and corrective action system (FRACAS), fault tree analysis (FTA) or other methods.
- Measures to inform users of any residual risks.
- A conclusion with evidence that the remaining risks are acceptable when compared to the benefits. This conclusion shall be dated and signed by senior management.
- Evidence that the risk analysis is part of the manufacturer's risk management plan (inclusion of documented evidence in this regard).
- Where a standard has been followed, identify the standard.

2.9 Essential Principles (EP) checklist

The product dossier will provide evidence of conformity to the "Essential Principles" as outlined in the IMDRF document IMDRF/GRRP WG/N47:FINAL[4] *Essential Principles of safety and performance of medical devices and IVD medical devices*.

Conformity to the Essential Principles shall be summarized in an Essential Principles checklist, a table that includes:

- Whether each Essential Principle applies to the product and if not, a justification for why this is not the case.
- The method used to demonstrate conformity with each relevant Essential Principle, as well as the reference for the method used.

[4] As amended from time to time

- A reference to specific technical documentation that demonstrates conformity to each relevant Essential Principle (where such documentation is specifically required for inclusion in the product dossier, its location in the product dossier shall be provided).
- Identification of specific standards or guidelines referenced, as appropriate.

2.11 Other submission context information

2.11.1 Global prices

In this section, the manufacturer shall provide both the global minimum and global maximum price of supply for the product (in US dollars) for the last financial year.

2.11.2 Training and support networks

The information provided in this section shall include:

- Detailed information about the training and support network that is available in each country of supply, including:
    - How the users are trained in the operation of the product
    - How the users of the product contact the supplier/manufacturer for technical support
- A statement as to whether there are representatives located in each country of supply to provide technical support; and if so, how many.

3. Analytical performance and other evidence

3.5 Analytical performance

Relevant WHO Technical Guidance:Series: See TGS-3 Principles of performance studies for additional detailed information.

3.5.1 Stability of specimen(s)

In this section, the manufacturer shall provide studies to support the stability, storage and where appropriate, transport, of all specimen type(s) identified in the labelling, including any and all recommended additives (e.g. anticoagulants). This information, presented as described in section C.4, shall include:

- Storage conditions (lower and upper limits of claimed temperature range, duration at each temperature, variation in humidity, freeze/thaw cycles).
- Transport conditions, where applicable.
- How the storage conditions, as well as the maximum allowable time between specimen collection and its processing, or addition to the IVD, takes into consideration the settings of intended use.
- Details of the specimen collection media, collection devices and transfer devices, whether these contain anticoagulants and whether they can be sealed, if applicable.

3.5.2 Validation of specimens

In this section, the manufacturer shall provide information regarding the types of specimens that can be used with the IVD.

The different specimen types that can be used with the product shall be identified, including detailed information for each matrix and anticoagulant, and whether contrived specimens have been used in the study, as applicable. The method used to generate contrived specimens shall be described. Specimen types claimed in the product dossier shall be consistent with those reported in the product IFU.

Evidence supporting claims of performance in each claimed specimen type (including anticoagulants) shall be provided as described in section C.4.

Depending on the product, information should be provided on the relationship of specimens collected by different methods (e.g. specimens that can be collected by a swab or by other means), as applicable.

The established relationship between product performance in claimed specimen types (e.g. plasma, blood, dried blood spots [DBS], etc) shall be considered in the design of subsequent studies. For example, if it is demonstrated that two or more claimed specimen types are equivalent, then not all specimen types need necessarily be tested in all subsequent studies. If there is no equivalence between claimed specimen types, then the impact that this will have on each subsequent performance claim shall be fully understood and described.

3.5.3 Metrological traceability of calibrator and control material values

In this section, the manufacturer shall provide detailed information about the traceability of values assigned to calibrators and trueness control materials supplied with the product (if applicable) and those used for the manufacturing process. Include, for example, methods and acceptance criteria for the traceability to reference materials and/or reference measurement procedures and a description of value assignment and validation.

***Note*:** Precision control materials used when establishing the reproducibility of a measurement procedure do not require the assessment of traceability to a reference material or a reference method.

3.5.4 Accuracy of measurement

While **measurement trueness**, affected by systematic error, is normally expressed as bias, and **measurement precision**, affected by random error, is naturally expressed as standard deviation, **accuracy** is affected by a combination of systematic and random effects that contribute as individual components of the total error of measurement.

3.5.4.1 Trueness

Trueness measures apply to both quantitative and qualitative assays only when a reference standard or method is available.

In this section, the manufacturer shall provide evidence that establishes the trueness of the product. Information shall be provided, as described in

section C.4, in sufficient detail to allow an understanding of the adequacy of the approach. Where this evidence has been generated as part of other performance evaluations, this evidence should be reported in the appropriate section of the product dossier and a reference to it made here.

3.5.4.2 Precision (repeatability and reproducibility)

In this section, the manufacturer shall provide evidence supporting claims for the precision of the product: i.e. repeatability (e.g. within-run variability) and reproducibility (e.g. between-run, -lot, -day, -operator, -site etc. variability, as appropriate). In addition to the information specified in section C.4, the studies provided in this section shall include:

- Estimation of precision for each analyte for which detection is claimed. A justification shall be given if this is not provided.
- Testing in a panel of specimens that reflects the main specimen types intended for use with the IVD.

For products that will be used at point-of-care, testing is likely to be undertaken by users who represent a diversity of skills, training and experience. This section should include studies where operator-to-operator variability has been investigated using representative of likely end-users of the product (e.g., non-laboratory trained personnel: healthcare workers and trained lay providers) using only those materials provided with the IVD (e.g. instructions for use, labels and other instructional materials) who have undertaken the testing unassisted, following only those instructions provided with the product. Personnel shall be selected who reflect the diversity of intended users and operational settings so as to challenge the usability of the product.

3.5.5 Analytical sensitivity

This section shall include evidence that demonstrates the analytical sensitivity of the product. Analytical sensitivity shall be determined for each claimed variant, type and/or subtype, where a suitable biological reference material exists. Depending on the intended use of the product this may include studies that establish limit of detection (LoD): the lowest concentration of analyte (measurand) in a specimen that can be reliably detected.

For a quantitative assay, identify the following parameters and provide details as to how they were derived:

- Limit of blank (LoB): the number of standard deviations above the mean value of the specimen without analyte (measurand).
- Limit of detection (LoD): the lowest concentration distinguishable from zero, based on measurements of specimens containing analyte (measurand).
- Limit of quantitation (LoQ): the lowest concentration at which precision and/or trueness are within specified criteria.

In addition to the information described in section C.4, studies that establish analytical sensitivity shall include:

- A description of specimen type and preparation, including the matrix used, the amount of analyte in each specimen and how this was established. Analytical sensitivity shall be demonstrated in a clinical sample matrix and shall use the entire assay system from sample preparation to interpretation.
- The number of replicates tested at each concentration.
- A description of the calculation used to determine assay sensitivity.

3.5.6 Analytical specificity

This section describes interference and cross reactivity studies to determine the analytical specificity of the product. Analytical specificity is defined as the ability of a measurement procedure to detect or measure only the analyte (measurand) to be detected, in the presence of other substances/agents in the specimen.

Substances with the potential to cause interference or cross-reactivity will vary depending on the assay type and design and may arise from either exogenous or endogenous sources. Typically, interference and cross-reactivity studies involve adding the substance under evaluation to the specimen and determining any bias of the test parameter relative to the control specimen to which no such substance has been added.

Analytical specificity shall be evaluated in relation to the potential not only to cause false positive results (using specimens that do not contain the analyte) but also to cause false negative results (using specimens with the analyte at or added to a low level of reactivity on the product).

Substances for which the potential for interference or cross-reactivity can be reasonably expected should be identified as part of a risk assessment for the product, taking into consideration the populations and settings in which the product will be used.

Common interferants and cross-reacting substances/agents may include, as appropriate:

- Substances used for patient treatment (e.g. therapeutic drugs, anticoagulants, etc.).
- Substances ingested by the patient (e.g. over the counter medications, alcohol, vitamins, foods, etc.).
- Substances added during specimen preparation (e.g. preservatives, stabilizers).
- Substances encountered in specific specimen types (e.g. haemoglobin, lipids, bilirubin, proteins).
- Analytes of similar structure (e.g. precursors, metabolites) or medical conditions unrelated to the test condition, including specimens negative for the assay but positive for a condition that may mimic the test condition (e.g. for a hepatitis A assay: specimens negative for hepatitis A virus, but positive for hepatitis B virus).
- Specimens from unrelated infections that cause false negative results.

- Substances used in, or related to, the design of the product: e.g. biotin and/or avidin; interference from human antibodies to components of the vector used for expression of product reagents.
- For WHO purposes, this would include consideration of other common infectious agents as well as related treatments for patients in resource-limited settings in WHO Member States, including those in Africa and Asia.

In this section, the manufacturer shall provide studies, as presented in section C.4, that evaluate the effects on the product of potentially interfering and cross-reacting substances/agents. These studies shall include:

- the substance/agent type, numbers of each corresponding specimen, and concentration tested
- specimen type
- measurand (e.g. analyte concentration)
- test results that are reported with respect to each condition (and analyte, as appropriate) and not reported as an aggregate of the total number of specimens tested in the study
- evidence that any observed interference or cross-reactivity is reported as a limitation of performance in the product IFU
- a study design that includes appropriate interferents and cross-reacting substances/agents.

3.5.7 High dose hook effect

In this section, the manufacturer shall provide evidence, as described in section C.4, that supports the absence of high-dose hook, or prozone effects (if applicable). Specimens used to investigate high dose hook effect shall be chosen that have a high analyte concentration, as determined using a method other than the product intended to be prequalified. This second method shall be of a design not subject to a prozone effect.

3.5.8 Measuring range of the assay

Relevant WHO Technical Guidance:Series: See TGS-6 Panels for quality assurance and quality control of in vitro diagnostic medical devices for additional detailed information.

This section provides information regarding studies that define the measuring range of the assay (linear and non-linear measuring systems), including the lower and upper limits of quantification (LLoQ and ULoQ), as appropriate, and describes information as to how this has been established. The extent of correlation of quantitation with a suitable reference test shall also be determined.

In this section, the manufacturer shall provide the studies and information identified in sections C.4 that allow an understanding of the approach and its validity.

3.5.9 Validation of assay cut-off

In this section, the manufacturer shall provide an explanation, with supporting evidence describing how the assay cut-off (or the algorithm/method for determining a cut-off for different assay runs) has been established (if applicable). Depending on the intended use of the product, this may require an explanation of the statistic approach (e.g. use of Receiver Operator Characteristics [ROC] curve). Evidence in this section shall be presented as described in section C.4.

For products that include the use of a test reader, the way in which the reader has been designed to differentiate reactive specimens from those that are non-reactive shall be demonstrated.

3.5.10 Validation of the assay procedure

In this section, the manufacturer shall provide a demonstration of how the assay procedure was validated, with regard to important reaction conditions (e.g. reaction times, reaction temperature, reagent volume, reading time,) and validation of controls (if applicable).

For example, for products where a reading interval is specified (i.e. time when result can first be read; time beyond which result should not be read), validation of critical time points shall be provided.

Evidence in this section shall be presented as described in section C.4. These studies may be conducted as part of investigations into the robustness of the product (see section 3.6.4 Usability/Human factors).

3.6 Other studies

3.6.1 Electrical systems: safety, mechanical and environmental protection, and electromagnetic compatibility

In this section, the manufacturer shall provide evidence of conformity to a recognised standard conducted by an accredited agency, such as a valid conformity certificate and report, if applicable.

3.6.2.8 Software testing as part of verification and validation

In this section, the manufacturer shall provide software validation reports that cover at a minimum:

- Verification of built-in fail safe
- Verification of alert mechanisms
- Verification of quantitative results detection
- Verification of quantitative results calculation
- Evidence to demonstrate that appropriate error codes are provided to the end user

3.6.3 Cleaning and disinfection validation

In this section, the manufacturer shall provide disinfection efficacy studies to demonstrate effectiveness of the chosen disinfectant, effectiveness of the cleaning and disinfection procedure, and evidence that the functionality

and analytical performance of the product is not reduced after multiple cycles of the cleaning and disinfection process.

3.6.4 Usability/human factors

In this section, the manufacturer shall provide studies that specifically assess the robustness of the product, a term that denotes a product's resilience to variations in either its environment or its usage.

Robustness (flex) studies consider the labelling and/or design of the product with respect to the potential impact of human behaviour, abilities, limitations and other characteristics on the ability of the product of fulfil its intended use. The impact of reagent variations is also considered.

Robustness studies should challenge the product under conditions of stress that allow an understanding of any potential product deficiencies, including where and how a product might fail. The manufacturer shall consider multiple skill levels of users, as well as potential instrument and reagent problems.

Depending on the intended use of the product and the manufacturer's risk assessment, the influence of the following factors should be included in this section:

- Operator error/ human factors, including use of incorrect specimen type, Incorrect application of the specimen to the device (e.g., incorrect placement, incorrect volume), incorrect handling of reagents including those in self-contained unitized test devices, incorrect placement of device (e.g., non-level surface), incorrect placement of reagents, including strips, or other components that contain reagent, use of incorrect reagents (for example, reagents that are not specific for the particular device or lot or generic reagents), incorrect order of reagent application, use of incorrect amount of reagent, incorrect timing of procedures (e.g., specimen application, running the test, or reading results), incorrect reading of test results, incorrect reading due to color blindness, etc..
- Specimen integrity and handling including errors in specimen collection, clotted specimens, error in specimen handling, incorrect specimen transport and/or storage, presence of bubbles in the specimen etc.
- Reagent integrity (reagent viability) including use of improperly stored reagents, use of outdated reagents, use of improperly mixed reagents, use of contaminated reagents, etc.
- Hardware, software, and electronics integrity including power failure, power fluctuation, incorrect voltage, repeated plugging and unplugging of the device, hardware failure, software failure, electronic failure, physical trauma to unit, etc.
- Stability of calibration and internal controls including factors that affect calibrator and calibration stability, and/or factors that may interfere with calibration.
- Environmental factors including impact of key environmental factors (temperature, relative humidity, barometric pressure changes, altitude

(if applicable), sunlight, surface angle, device movement, etc.) on reagents, specimens, and test results, impact of key environmental factors (including changes in parameters such as pH or temperature) etc.

In addition to the requirements summarized in section C.4, the studies in this section shall include:

- A summary of the evidence that falls within this category
- Testing in specimens that represent all relevant test results and/or interpretations (e.g. reactive and non-reactive; enzyme deficiency at key decision points, etc.)
- Details of the test environment and relation to the intended use environment
- A discussion of what tests were considered for the device and why they were or were not performed
- A discussion to demonstrate why the evidence presented is sufficient to support the application

Depending on the product (e.g. products likely to be used in point-of-care settings by users with limited training, skills and/or experience) this section shall include studies, as described in section C.4, that demonstrate:

- Label comprehension - questionnaire-based testing of subjects representative of end users undertaken to assess the ability of intended users to correctly comprehend key messages from packaging and labelling.
- Interpretation of results – testing to assess the ability of subjects to correctly interpret contrived test results.

Manufacturers are reminded to refer to the corresponding TSS to understand the requirements for usability studies relevant to their product.

If a clinical study has been conducted that includes usability/human factor endpoints (e.g. for self-testing), reference to the studies and endpoints shall be made in this section but full results do not need to be repeated here and shall be included in chapter 4 – clinical evidence.

3.6.5 Stability of the IVD

Relevant WHO Technical Guidance:Series: See TGS-2 Establishing the stability of an IVD, *Annex to TGS 2 Establishing component stability for in vitro diagnostic medical devices* and TGS-3 Principles of performance studies for additional detailed information.

This section describes claimed shelf life (including transport stability) as well as in-use stability of a product.

Claims for stability shall be based on the second-last successful data point from the least stable lot. For example: for testing conducted at 3, 6, 9, 12 and 15 months, if stability was observed at 15 months, then the maximum stability claim can be 12 months.

Each of the studies referred to in section 3.6.5 for product stability must be presented as described in section C.4. In addition to specifying acceptance

criteria, the study protocol must specify appropriate testing intervals and ensure that testing extends beyond the projected claim of shelf life.

***3.6.5.1** Claimed shelf life*

In this section, the manufacturer shall provide information and studies that support the claimed shelf life of the product. Determination of product shelf life shall be preceded by a simulated transport challenge using storage conditions that mimic environmental conditions likely to be encountered in resource-limited WHO Member States.

The product lots used for shelf life determination shall be equivalent to routine production. Product lots shall be in their final configuration, if the product is available in different configurations, testing shall be conducted on all configurations.

The final claim of shelf life shall be based on real-time stability testing. Claims of shelf life from accelerated studies may be accepted as preliminary estimates, provided real-time studies are underway. The method used to estimate shelf life from accelerated data shall be provided.

3.6.5.2 In-use stability

In this section, the manufacturer shall provide information, as described in section C.4, establishing the in-use stability of each labile component in the product. Depending on the product this may include: test cartridge, buffer, conjugate, substrate, stopping solution and other prepared, or reconstituted working reagents.

In-use stability shall reflect actual routine use of the device (real or simulated)**.** Depending on the product, this would include open vial stability and/or, for automated instruments, on-board stability. Consideration shall be given to multiple accessing of reagent bottles or plate pouches (opened several times during its use).

In the case of automated instrumentation, if calibration stability is claimed, then supporting data shall be included.

3.6.5.3 Shipping stability

This section describes evidence in support of claims that the product is not affected by the extremes of conditions likely to be encountered during transport to the end-user once a product has been manufactured.

It is expected that a product is subjected to a simulated shipping challenge before commencing real-time shelf life determination (see section 3.6.5.1). Consequently, a separate shipping stability study is not necessarily required in this section.

If a separate shipping stability study is provided in this section, please refer to study requirements summarized in sections C.4, 3.6.5 and 3.6.5.1.

In this section, the manufacturer shall provide information and studies that demonstrate that the product, in its final packaging, has been subjected to drop-shock testing.

3.8 Other evidence

3.8.1 Testing in performance panels and other TSS-specific evidence

Depending on the intended use of the product, the corresponding TSS may stipulate requirements for additional studies that establish particular claims for product performance. These may include studies that demonstrate antibody neutralization (e.g. for IVDs with a confirmatory function), performance at critical decision points and/or testing in performance panels, such as:

- Seroconversion panels.
- Genotype panels.
- Subtype panels.
- Mixed-titre panels.

In this section, the manufacturer shall provide information, as described in section C.4, that demonstrates performance of the product according to specific TSS requirements.

4. Clinical evidence

Clinical evaluation is the assessment and analysis of data generated from the clinical intended use of the product in order to verify the clinical safety and performance of the device. Clinical evidence is the combined information from the clinical data and its evaluation. A manufacturer shall have clinical evidence to support any clinical claims. This will include claims for clinical or diagnostic sensitivity and specificity.

4.2 Overall clinical evidence summary

Relevant WHO Technical Guidance:Series: See TGS-3 Principles of performance studies for additional detailed information.

In this section, the manufacturer shall provide a brief (1-2 page) summary of the available clinical evidence being presented in support of the submission. The document should list the evidence presented, its characteristics and provide a discussion of how this is considered sufficient to support request for marketing for the requested indications. A tabular listing of clinical studies may be included in this section. This section should also include a discussion to support why the evidence presented is sufficient to support the application.

4.2.1 Expected values/reference ranges

If applicable, the manufacturer shall provide in this section information regarding what values to expect in healthy individuals versus those in individuals affected by a corresponding infection, disease and/or condition.

4.2.3 IVD medical device specific clinical studies

All claims for the clinical performance of the product shall be supported by well-designed performance evaluations. These may include evaluations that have been carried out or coordinated by the manufacturer, as well as evaluations carried out by bodies wholly independent of the manufacture.

In addition to the information described in section C.4, clinical evaluation studies provided in this section shall include:

- Any anomalous results, or results that are not within predetermined specifications, shall be clearly explained or justified. All invalid results shall be recorded and evaluated in comparison to the reference result. Invalid results shall not be excluded from estimates of sensitivity or specificity.
- Estimates of diagnostic/clinical sensitivity and specificity shall be reported with 95% confidence intervals.
- Where an IVD is intended to detect multiple analytes without differentiating which analyte is detected, specimens chosen for the testing panel shall comprise those that are reactive only for each individual analyte.
- Results shall be reported with respect to each study site and not be reported as an aggregate of the total number of specimens tested to establish these characteristics.
- Details of the product lots/batches used for the evaluation, including lot number, date of expiry, and the storage conditions of the product before and during the study.
- Details of the geographical region, clinical status, age and sex, as appropriate, of the subjects from which specimens have been drawn for the clinical evaluation.
- Full details of the method used to select specimens for testing that would allow it to be understood that selection biases have been either minimized or eliminated. This shall include any acceptance/exclusion criteria as well as details of any specimens that were excluded from selection using these criteria.
- Full details of the methods used to define the clinical status of the subjects and to characterize the specimens.
- Evidence that the outcomes of the performance studies have been reviewed by the manufacturer's management and accepted for implementation.
- All abbreviations used in reports and on data records shall be explained and clearly defined.
- If the study has been published in peer-reviewed scientific literature, provide publication details for the study.
- Testimonials from hospitals, laboratory staff, product users, patients, or testimonials of any other kind are not considered to be evidence of performance. Testimonials shall not be included in the dossier as they will not be considered during review.

4.7 Other clinical evidence

4.7.1 Qualification of usability

Depending on the intended use of the product (e.g. self-testing), the corresponding TSS may stipulate a requirement for clinical evaluation of the

usability of the product. In this section, the manufacturer shall provide information, as described in section C.4, that demonstrates the performance of the product when used by observed, untrained self-testing users.

5. Labelling and promotional material

5.2 Product/package labels

In this section, the manufacturer shall provide all packaging labels used in the product. This includes primary and secondary labelling of all devices, accessories and components (but exclusive of labels for shipping). Labels shall include at least the following information:

- The product name and product identification number (product code/catalogue number).
- The name and contact details of the manufacturer, or an authorized representative of the manufacturer, on the outer package labels.
- The name of the reagent/ingredient.
- The expiry date (or a statement as to where and how this will be displayed).
- An indication of any special storage and/or handling conditions that apply.
- The warnings and precautions.
- The lot/batch and/or serial number (or a statement as to where and how this will be displayed).
- The information regarding product conditions such as product sterility.
- The names of all included reagents in each box on the outer package label, where possible.
- If a component is too small to contain all the above information, it shall at a minimum contain the name, lot number expiration date, volume, and storage conditions.
- If the product requires associated instrumentation, the requirements listed above also apply to the instrument.

5.3 Package insert/instructions for use

Relevant WHO Technical Guidance:Series: See TGS-5 Designing instructions for use for in vitro diagnostic medical device for additional detailed information.

In this section, the manufacturer shall provide the current product IFU. The information provided in a product IFU shall be clear, correct, suitable for intended users and consistent with that provided in the product dossier.

The product IFU shall at a minimum include the following information:

- Product identification (name of the product and variants and corresponding product codes)
- A clearly stated intended use, including:

    - What is detected by the assay (that is, the analytical use of the assay e.g. the marker or nucleic acid sequence being detected).
    - The clinical indication for the test (e.g. if it is for a specific disorder, or a condition or risk factor of interest that the test is intended to detect, define or differentiate).
    - The function of the product (screening, monitoring, diagnostic or aid to diagnosis, staging or aid to staging of disease).
    - The intended user (self-tester, laboratory professional and/or at point-of-care).
    - The intended testing population (e.g. neonates, antenatal women).
    - The type of specimen(s) required (e.g. serum, plasma, whole blood, sputum, urine).
    - Whether the assay is automated.
    - What the instrument is intended for.
    - Whether the test is qualitative or quantitative.
    - An indication that the product is for in vitro use.
- A general description of the principle of the assay method or instrument principles of operation.
- A description of all components of the assay (e.g. reagents, assay controls and calibrators) and a description of the reactive ingredients of relevant components (e.g. antibodies, antigens, nucleic acid primers etc.)
- A description of the specimen collection and transport materials provided with the product or recommended for use.
- For instruments of automated assays: a description of the appropriate assay characteristics or dedicated assays.
- For automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation.
- If applicable, a description of any software to be used with the product.
- If applicable, a description or complete list of the various configurations/variants of product that will be made available.
- If applicable, a description of the accessories, and other products that are intended to be used in combination with the product but are not provided with the product.
- Storage conditions, including storage conditions and stability of both the unopened and opened product, and working solutions. When applicable, these instructions shall include such information as conditions of temperature, light, humidity, and other pertinent factors
- Specimen exclusion criteria (e.g. specimens with visual evidence of hyperlipidaemia or haemolysis, excessive specimen age, excessive number of freeze/thaw cycles).

- If the test kit includes sterile accessories, an indication of that condition and any necessary instructions in the event of damage to sterile packaging.
- If the test kit includes accessories that have been specified by the manufacturer as intended for single-use only, an indication of that status.
- Clear instructions on how to perform the assay, including instructions on specimen collection, handling, preparation and storage of reagents, the use of assay calibrators and controls as well as the reading and interpretation of test results.
- Recommendations for quality control procedures.
- Clear instructions on the correct usage of any equipment or software that is required for the performance of the assay.
- Any warning and precautions to be considered related to the use of the assay including but not limited to interpreting the results, the disposal of the assay and/or its accessories (e.g. lancets), to any consumables used with it (e.g. reagents) that may be carcinogenic, mutagenic or toxic, or to any potentially infectious substances of human or animal origin.
- Any residual risks.
- Precautions and measures to be taken in the event of performance changes or product malfunction.
- Limitations of the assay, including information about interfering substances that may affect the performance of the assay.
- Performance characteristics including diagnostic sensitivity and specificity, seroconversion sensitivity, accuracy, dynamic range, limit of detection, and reproducibility, as appropriate, and any other performance aspects that are relevant to the product.
- Any requirements for special training or particular qualifications of the assay user.
- Any requirements for routine maintenance. Include details of frequency of maintenance and who should perform this maintenance (for example: the user, a representative of the manufacturer, or a third party).
- Where relevant, a bibliography.
- Document control details, such as a document version number and release date.
- Definition of terms and abbreviations (if applicable).
- The name and contact details of the manufacturer or an authorized representative of the manufacturer, in order for the user to obtain assistance.

5.6 Technical and/or operators manual

If the product requires associated instrumentation, include a copy of the

instrument manual and/or associated operator manuals.

5.8 Other labelling and promotional material

Provide copies of any other instructional materials that are provided to the user such as job aids, information resources on a website, CD-ROM etc.

6. Quality management system

6.6 Quality management system

An effective quality management system is a key consideration for all manufacturers of IVDs. Therefore, products submitted for prequalification assessment shall be manufactured under an appropriate quality management system. The manufacturer's quality management system shall cover all sites used to manufacture this product.

The quality management standard *ISO 13485*[5] *Medical devices — Quality management systems — Requirements for regulatory purposes* is a benchmark in quality management for manufacturers of IVDs for regulatory authorities throughout the world. WHO Prequalification bases its product dossier assessment and inspection processes on the requirements of this internationally-recognized quality management standard.

In this section, the manufacturer shall provide high level quality management system procedures for establishing and maintaining the quality management system, including a copy of the current version of the manufacturer's quality manual. The following aspects shall be addressed (or referred to) in the quality manual:

- title and scope
- table of contents
- review, approval and revision
- quality policy and objectives
- organization, responsibility and authority
- references
- quality management system description
- appendices
- document control information relevant to the quality manual, including version number, release date and approval record

Also, provide the documented procedure(s) relevant to risk management planning and implementation and a list of current quality management procedures.

6.8 Resource management procedures

In this section, the manufacturer shall provide:

- A staff organogram.
- The number of employees at the manufacturing site.

[5] As amended from time to time

6.9 Planning of product realization and customer related procedure

In this section, the manufacturer shall provide high level product realization procedures such as those addressing planning and customer related processes.

6.10 Design and development

In this section, the manufacturer shall provide procedures that document the systematic and controlled development of product design from initiation of a project to transfer to production, including those relevant to change control/change notifications [product and processes]). This shall include information regarding the design processes specific to the product under assessment, including a flowchart of the design process that outlines design inputs and outputs for the product. If design takes place at multiple sites, the controlling site shall be identified.

6.11 Purchasing

In this section, the manufacturer shall provide procedures that document that purchased products/services conform to established quality and/or product specifications, including those relevant to the evaluation and control of key suppliers and verification of purchased product/services.

6.12 Production and service controls

In this section, the manufacturer shall provide:

- A description of the manufacturing site(s), including:
    - Full address(es), including latitude and longitude of the manufacturing facility(s).
    - A site master file, with a diagram of the floor plan, highlighting production areas.
- A flow chart of the entire manufacturing process including in-process control points.
- Details of each major step (including in–process control points and final product testing and packaging) in the manufacturing process.
- An overview of verification, validation, and quality control activities for all stages of design and manufacture (including purchased components, in-process products, and finished products).
- A list of critical raw materials (including details and address of the supplier of outsourced materials and their corresponding certificates of analysis).
- The batch release criteria for the product under assessment as well as documented procedures for how these were determined.
- A list of outsourced processes with direct product impact, for example:
    - manufacturing of components and/or accessories (conjugated antibodies, strips, reagents, lancets…),
    - laboratory testing, packaging, printing, etc., including details of the supplier for each process.
        - If the key supplier holds a certificate issued by a conformity assessment body, and it is related to the quality management

system, annex certified copies to the dossier. If there are no such certificates, state this.

- A description of any other manufacturing that occurs at each site.

6.14 QMS measurement analysis and improvement procedures

In this section, the manufacturer shall provide procedures that document monitoring, measurement, analysis and improvement to ensure the conformity of the product and QMS, and to maintain the effectiveness of the QMS, including those relevant to control of nonconforming goods/processes and complaint handling and vigilance.

7. Relevant documents

The following documents and webpages provide information to guide the manufacturer through WHO's prequalification assessment.

- https://extranet.who.int/prequal/vitro-diagnostics
- Pre-submission form. Geneva: World Health Organization; (PQDx_015).
- Instructions for completion of the pre-submission form. Geneva: World Health Organization; (PQDx_017).
- Product dossier checklist. Geneva: World Health Organization; (PQDx_049).
- Prequalification of in vitro diagnostics Technical Specification Series available on WHO's website https://extranet.who.int/pqweb/vitro-diagnostics/technical-specifications-series
- Prequalification of in vitro diagnostics Technical Guidance series available on WHO's website https://extranet.who.int/prequal/vitro-diagnostics/technical-guidance-series
- International Medical Device Regulators Forum (IMDRF) documents available on the IMDRF website https://www.imdrf.org/documents
- ISO 13485 Medical devices – Quality management systems – Requirements for regulatory purposes. Geneva: International Organization for Standardization. Available to purchase on the ISO website https://www.iso.org/iso-13485-medical-devices.html

8. Contact information

Any inquiries regarding WHO's prequalification of in vitro diagnostics should be addressed to: *diagnostics@who.int*

Annex 1 – Abridged product dossier requirements

Abridged product dossier content requirements
1. REGIONAL ADMINISTRATIVE
1.1 Cover letter
1.2 Submission table of contents
1.3 List of terms/acronyms
1.4 Application form/administrative information
1.5 Listing of device(s)
1.6 QMS or other regulatory certificates
1.7 Free sale certificate/certificate of marketing authorisation
1.8 User fees
1.12 Statements, certifications, declarations of conformity
2. SUBMISSION CONTEXT (Product Information)
2.4 Device description
2.4.1 Comprehensive device description and principle of operation
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 (commercial history)
2.6.1 Global market history
2.6.4 Evaluation/inspection reports issued by the Recognized Regional Authority, if available
2.8 Risk management
2.11 Other submission context information
2.11.1 Global prices
3. Analytical performance and other evidence
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 or/and operators manual
5.8 Other labelling and promotional materials

Annex 2 Example declaration of authenticity

This declaration should appear on the front page of the document being certified or notarized.

Declaration of authenticity

I, the undersigned, as a …….. …….. for the state of ……., country……..

Declare that the attached copy of the document issued by ……..and certified by me, is a true and accurate copy of an original document presented to me for certification.