



INSTRUCTIONS FOR COMPILATION OF A PRODUCT DOSSIER

Prequalification of Diagnostics

Table of Contents

1. Introduction	4
2. Intended Audience	5
3. The Product Dossier	5
3.1. About the product dossier	5
3.2. Submission of a product dossier	6
4. Dossier Format	7
4.1. Dossier clarity	7
4.2. Layout and order	7
4.3. Language and units of measure	8
5. The Product	8
5.1. Regulatory versions of this product	8
5.2. Product description including variants (configurations) and accessories	8
5.3. Essential principles (EP) checklist	9
5.4. Risk analysis and control summary	10
6. Design and Manufacturing Information	10
6.1. Product design	10
6.1.1. Design overview	10
6.1.2. Formulation and composition	11
6.1.3. Biological safety	11
6.1.4. Documentation of design changes	11
6.2. Manufacturing processes	11
6.2.1. Overview of manufacture	11
6.2.2. Sites of manufacture	11
6.2.3. Key suppliers	12
7. Product Performance Specification, and Associated Validation and Verification Studies	12
7.1. Analytical studies	13
7.1.1. Specimen type	13
7.1.2. Analytical performance characteristics	14
7.1.2.1. Accuracy of measurement	14
7.1.2.2. Analytical sensitivity	15
7.1.2.3. Analytical specificity	15
7.1.2.4. Metrological traceability of calibrators and control material values	16
7.1.2.5. Measuring range of the assay	16
7.1.2.6. Validation of assay cut-off	16
7.2. Stability (excluding specimen stability)	17
7.2.1. Claimed shelf life	17
7.2.2. In use stability	17
7.2.3. Shipping stability	18
7.3. Software verification and validation	18
7.4. Clinical evidence (clinical or diagnostic sensitivity and specificity)	18
7.4.1. Clinical evaluation - Manufacturer	18
7.4.2. Clinical evaluation - Independent study	19
8. Labelling	20

8.1. Labels.....20
8.2. Instructions for use20
9. Commercial History22
9.1. Countries of supply22
9.2. Adverse events and field safety corrective actions22
10. Regulatory History23
11. Quality Management System24
11.1. Quality manual24
11.2. Quality management system documents24
11.3. Quality management system certification.....25
12. Contact Information25
13. Reference Documents.....25
14. Annex A - Essential Principles (EP) checklist.....27

1. Introduction

The World Health Organization (WHO) Prequalification of Diagnostics Programme is coordinated through the Diagnostics and Laboratory Technology Team (DLT), in the department of Essential Health Technologies (EHT). The aim of the WHO Prequalification of Diagnostics Programme is to promote and facilitate access to safe, appropriate and affordable diagnostics of good quality in an equitable manner. Focus is placed on diagnostics for high burden diseases and their suitability for use in resource-limited settings.

The WHO Prequalification of Diagnostics Programme undertakes a comprehensive assessment of the submitted products through a standardized procedure which is based on WHO prequalification requirements. The prequalification of diagnostics process includes three main components:

- review of an application form and product dossier;
- laboratory evaluation of the product; and
- inspection of the manufacturing site(s).

Another element of the WHO Prequalification of Diagnostics Programme is the strengthening of the regulatory capacity of WHO Member States to improve pre- and post-market regulatory oversight of diagnostics.

The findings of the WHO Prequalification of Diagnostics Programme are used to provide technical information principally to other United Nations (UN) agencies, but also to WHO Member States and other interested organizations, on particular diagnostic technologies.

The prequalification status of diagnostics, in conjunction with other procurement criteria, is used by UN agencies, WHO Member States and other interested organizations to guide their procurement of diagnostics.

Prequalification does not imply any approval by WHO of the diagnostic products and manufacturing site(s) in question (which is the sole prerogative of national regulatory authorities). Moreover, prequalification does not constitute any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety and/or efficacy in the diagnosis of specific diseases.

2. Intended Audience

This document has been prepared to assist manufacturers¹ in correctly compiling a product dossier for the purposes of WHO prequalification assessment.

Manufacturers who wish to submit a product dossier for a diagnostic should read this document carefully and compile the product dossier in accordance with the requirements prescribed below.

3. The Product Dossier

3.1. 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 diagnostics, WHO will use the term the *product dossier*, or simply the *dossier*.

The manufacturer is expected to prepare, and either hold or provide timely access to, technical documentation that shows how each diagnostic was developed, designed and manufactured. This technical documentation, typically controlled in the manufacturer's quality management system (QMS), is often extensive and sections of it may be held in different locations. The documentation is revised to reflect any changes made during the life cycle of the diagnostic through normal application of the manufacturer's QMS.

The product dossier is a selection of records and documents from this entire collection of records and documents that a manufacturer holds for a particular product. Manufacturers compile a product dossier from their existing technical documentation to provide evidence that the diagnostic conforms to the *Essential Principles of Safety and Performance of Medical Devices*². The information provided may include, for example, abstracts, high level summaries, or existing controlled documents, as appropriate, sufficient to communicate key relevant information and allow a reviewer to understand the subject to assess the validity of that information. Furthermore, the dossier should contain an *Essential Principles checklist (EP checklist)*. The content of the submitted product dossier should be traceable by the manufacturer for future reference.

¹ For the purposes of prequalification of diagnostics, the following definition applies: **Manufacturer** means any natural or legal person with responsibility for design and/or manufacture of a diagnostic with the intention of making the diagnostic available for use, under his name; whether or not such a diagnostic is designed and/or manufactured by that person himself or on his behalf by another person(s).

² The Global Harmonization Task Force document **GHTF/SG1/N41R9:2005 Essential Principles of Safety and Performance of Medical Devices** can be used as guidance document providing requirements of safety and performance. This document can be accessed through the following website: <http://www.gh tf.org/sg1/sg1-final.html>

The EP checklist should be created as part of the manufacturer's technical documentation and should be controlled by the manufacturer's QMS. It provides a tabular overview of the Essential Principles and identifies those that are applicable to the diagnostic, the chosen method of demonstrating that the device conforms to each relevant Essential Principle and the reference of the controlled document that is relevant to a specific Essential Principle. While many controlled documents are referenced in the EP checklist, only some may be contained within the product dossier. The cited references to the controlled documents also allow easy identification of additional relevant documents and data.

This document describes the elements that a product dossier is expected to contain for the purposes of the WHO prequalification of diagnostics process. These WHO product dossier requirements are in-line with those expected by a number of National Regulatory Authorities. However, as WHO is not a regulator, certain requirements of particular Member States may not be addressed in the product dossier prepared for the WHO prequalification of diagnostics process.

WHO reviews the product dossier with the purpose of:

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

The WHO decision on whether to continue the prequalification assessment to the laboratory evaluation and manufacturing site inspection stages is based on the review of the dossier.

NOTE: Information that was previously submitted in the *Prequalification of Diagnostics - APPLICATION FORM: Document PQDx_015* will be considered during the review of the product dossier. Therefore, manufacturers should ensure that the content of the product dossier is consistent with the information submitted in the application form and that any changes in the information submitted with the respective application form are promptly notified to WHO. Furthermore, inadequacies identified at the application form stage and communicated by WHO to the manufacturer are expected to be addressed as part of the dossier submission.

3.2. Submission of a product dossier

If an application to the WHO Prequalification of Diagnostics Programme has been accepted for prequalification assessment, the manufacturer is notified. Subsequently, a formal letter of agreement is sent by WHO to the manufacturer. This document should be duly signed and sent back to WHO and a non-refundable prequalification assessment fee of US \$12,000.- levied before the process can proceed further. Upon completion of these requirements, WHO formally requests the manufacturer to submit a product dossier. This formal WHO request includes instructions on where to send the product dossier.

NOTE: Manufacturers should not submit a product dossier to WHO unless requested to do so. Dossiers that are submitted without a request from WHO will not be given priority, and the dossier may be returned to the manufacturer without review.

Manufacturers should ensure that the dossier contains all the information as is prescribed in this document. The prequalification procedure may be terminated if the dossier does not contain the prescribed information, or where the information supplied is inadequate to complete the prequalification assessment effectively or where the requested information is not provided by the manufacturer within a specified time period.

4. Dossier Format

4.1. Dossier clarity

A review of WHO processes has identified that poor-quality dossiers take much longer time for assessment. Therefore, product dossiers should be clear and well-organized to ensure that the prequalification assessment procedure is efficient for all applicants.

Poorly prepared dossiers may be returned to the applicant without full review. It is important to keep the needs of the review staff in mind when preparing the product dossier for submission. This will ensure that the request can be reviewed as quickly as possible.

4.2. Layout and order

Submissions formatted according to the WHO requirements prescribed in this document are preferred. However, submissions previously prepared for various National Regulatory Authorities may be accepted if all the information required by WHO is supplied, and if the information is fully cross-referenced to the WHO prequalification of diagnostics requirements using the *Product Dossier Checklist* document PQDx_049.³

When submitting the product dossier, the following requirements should be fulfilled by the manufacturer:

- WHO requires two hard-copies of the dossier and one electronic-copy (CD or DVD) of the entire dossier.
- The hard-copy dossiers should be provided bound or in a ring-binder. If the dossier comprises multiple volumes, the volumes should be clearly marked *1 of 2, 2 of 2* etc.
- The hard-copy should be clearly divided into sections, as prescribed in the *Product Dossier Checklist*, and the pages of each section should be numbered.
- The hard-copy should include a table of contents.
- The dossier should be submitted using the Product Dossier Checklist (document PQDx_049) as the first page. All sections of the dossier should be cross-referenced to this first page.

³ This document may be accessed through the following website:
http://www.who.int/diagnostics_laboratory/evaluations/PQDxInfo/en/index.html

- The electronic copy of the dossier should be identical to the hard-copies in regard to content.

NOTE: The prequalification assessment process may be terminated if the dossier does not include the information prescribed in this document.

4.3. Language and units of measure

For the purposes of prequalification of diagnostics the following requirements apply:

- The dossier will be reviewed as an English language document.
- All documents presented in the dossier should be submitted in English (unless other arrangements have been made with WHO prior to submission of the dossier).
- Any translations of documents should be carried out by a certified translator. Details of the translator should be provided. The original and the translated document should be provided.
- Metric units shall be used, except where there are other internationally accepted units of measurement.

5. The Product

5.1. Regulatory versions of this product

Different regulatory requirements apply to different international markets for diagnostics. Manufacturers who supply a diagnostic into multiple countries often alter some aspects of a single product to comply with such varying regulatory requirements (for example: varied information within the instructions for use, different intended purpose statements, different batch release procedures, or different information on package labels).

If this product has multiple regulatory versions, the manufacturer should provide information regarding these different regulatory versions. This information should cover all aspects that are different between these product regulatory versions including (but not limited to) differences in design, manufacturing, quality control, release for supply, and post-market practices.

NOTE: If the product has multiple regulatory versions, the information included in the product dossier should clearly indicate which regulatory version of the product is submitted for prequalification assessment.

5.2. Product description including variants (configurations) and accessories

The dossier should include the following product descriptive information:

1. The intended use of the diagnostic. This may include:
 - a) what is detected
 - b) the function of the product (e.g. screening, monitoring, diagnostic or aid to diagnosis, staging or aid to staging of disease);
 - c) the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;
 - d) whether the product is automated or not;

- e) whether the test is qualitative or quantitative.
 - f) the type of specimen(s) required (e.g. serum, plasma, whole blood, sputum, urine);
 - g) the intended testing population (e.g. neonates, antenatal women).
2. The intended user (laboratory professional and/or at point-of-care);
 3. A general description of the principle of the assay method or instrument principles of operation.
 4. 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 (such as antibodies, antigens, nucleic acid primers).
 5. A description of the specimen collection and transport materials provided with the product or descriptions of specifications recommended for use.
 6. For instruments of automated assays: a description of the appropriate assay characteristics or dedicated assays.
 7. For automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation.
 8. If applicable, a description of any software to be used with the product.
 9. If applicable, a description or complete list of the various configurations/variants of product that will be made available.
 10. If applicable, a description of the accessories, and other products that are intended to be used in combination with the diagnostic.

The instructions for use may be used to provide some of this information on the condition that a cross-reference to the different requirements is supplied in conjunction with the instructions-for-use.

5.3. Essential principles (EP) checklist

The product dossier should include an EP checklist that identifies:

- the Essential Principles of Safety and Performance;
- whether each Essential Principle applies to the diagnostic and if not, why not;
- the method used to demonstrate conformity with each Essential Principle that applies; and
- the reference to the actual technical documentation that offers evidence of conformity with each method used.

The method used to demonstrate conformity may include one or more of the following:

- conformity with recognized or other standards;
- conformity with a commonly accepted industry test method (reference method);
- conformity with appropriate in-house test methods that have been validated and verified;
- comparison to a diagnostic already available on the market.

The EP checklist should include a cross-reference to the location of such evidence both within the full technical documentation held by the manufacturer and within the dossier (when such documentation is specifically required for inclusion in the dossier as outlined in this instructions).

A sample EP checklist is included in Annex A.

PQDx_018 v1 06.05.2010

5.4. Risk analysis and control summary

A risk analysis should be undertaken to identify and address all known or foreseeable hazards⁴ for the product, taking into account such aspects as the user/s of the device, and the technology involved. The dossier should contain a summary of the risks identified during the risk analysis process and a description of how these risks have been controlled to an acceptable level. Furthermore, the risk analysis should be part of the manufacturer's risk management plan.

Where specific standards or guidelines are recommended by WHO, these should be followed.

The information provided in the dossier should address possible hazards for the diagnostic such as the risk from false positive or false negative results, indirect risks which may result from product-associated hazards, such as instability, which could lead to erroneous results, or from user-related hazards, such as reagents containing infectious agents.

The results of the risk analysis should provide a conclusion with evidence that remaining risks are acceptable when compared to the benefits.

If the manufacturer holds a certificate issued by a conformity assessment body and related to risk management of the product under assessment, certified copies should be annexed to the dossier.

6. Design and Manufacturing Information

This section of the dossier should provide an overview of the design and manufacturing processes for the product under assessment, including a flow chart of the entire process. If design and manufacture is carried out at different sites, or by external suppliers, this should be indicated on the flow chart. The manufacturer should only refer to sites of suppliers of raw materials involved in critical design and manufacturing activities.

Where Quality Management System certificates, or the equivalent, exist for any sites, certified copies should be annexed to the dossier.

6.1. Product design

6.1.1. Design overview

The dossier should contain information to allow a reviewer to obtain a general understanding of the design applied to the product. It should include a description of the critical ingredients of an assay such as antibodies, antigens, enzymes and nucleic acid primers, provided or recommended for use with the product.

If design takes place at multiple sites, a controlling site should be identified.

⁴ Examples of possible hazards and contributing factors associated with diagnostics are given in the ISO 14971:2000(E).
PQDx_018 v1 06.05.2010

6.1.2. Formulation and composition

For each of the ingredients, provide formulation/composition information. For example, include information such as nucleic acid sequences for primers, ingredient lists for buffers, amino acid sequence details for recombinant proteins, etc.

Identify the sources of the materials from which the components are constructed.

6.1.3. Biological safety

List all biological components included in the product under assessment. This should include material of bacterial, viral, parasitic, animal, or human origin, such as plasma, cells, tissues, or their derivatives. The list should include:

- the name of the biological component
- details of the use of the biological component in the product
- description of steps taken for the reduction of transmission or infection risk.

Wherever possible, manufacturers should look to internationally accepted methods for reducing - and determining residual risk of - transmission or infection risk from biological agents. Where specific standards or guidelines are recommended by WHO, these should be followed.

6.1.4. Documentation of design changes

The dossier should include records of each design change and the reasons for these, together with any associated validation/verification data. The documentation should include evidence for believing that the change achieves the desired effect, and that the product continues to comply with the Essential Principles of Safety and Performance.

6.2. Manufacturing processes

6.2.1. Overview of manufacture

The dossier should contain information to allow the reviewer to obtain a general understanding of the manufacturing process. This section is not intended to take the place of more detailed information required for a QMS audit or other conformity assessment activity.

The manufacturer should provide details of each major step in the manufacturing process, to clarify the manufacturing steps. Include information on the manufacturing process for all components. The information may take the form of a process flow chart showing, for example, an overview of production including the technologies used, assembly, any in-process and final product testing, and packaging of the finished product.

Details of verification, validation and quality-control activities should be provided for all stages of design and manufacture (including purchased components, in-process products, and finished products).

6.2.2. Sites of manufacture

A list of all critical manufacturing sites that are involved in the manufacture of this product should be provided. This should cover all stages of manufacture (including design,

warehousing, and quality-control stages of manufacture), but may not need to include the sites of supply of raw materials if they are not considered critical. For each site include:

- the name of site;
- the physical address of the site;
- a description of the component manufacture/stage of the manufacturing process carried out at the site;
- a description of the manufacturing site;
- a simple site plan highlighting production areas;
- the number of employees at the site;
- a description of any other manufacturing that occurs at this site.

NOTE: If a product is successfully prequalified, only product manufactured at the sites that have been presented in the product dossier will be considered to be prequalified. Any changes to sites of manufacture should be notified to WHO prior to implementation of the changes.

6.2.3. Key suppliers

List all key suppliers which supply ingredients/products/services for the manufacture of this product. For each supplier include:

- a description of the ingredient/product/service supplied;
- the name of the supplier;
- the physical address of the supplier's manufacturing facilities;
- details of the documented procedures used for the purchasing and verification of ingredients/products/services sourced from these suppliers.

If the manufacturer holds a certificate issued by a conformity assessment body and related to the quality management system, certified copies should be annexed to the dossier.

NOTE: WHO should be notified of all variations made to a prequalified product. This includes changes of key suppliers and components/products/services provided by key suppliers.

7. Product Performance Specification, and Associated Validation and Verification Studies

WHO requires the manufacturer to have carried out relevant investigations to support any performance claims such as analytical and clinical sensitivity and specificity, accuracy, repeatability, reproducibility, detection limits, and traceability. Investigations should also have been undertaken to assess the potential effects of interfering factors and claims of reagent and product stability.

Such performance evaluations may be based upon pre-existing data, scientific literature, or new studies carried out for the purpose of setting (validating) or verifying performance claims. Where data does not directly relate to the product, but for example, to similar products, a rationale explaining the relationship of the product to that used in the study should accompany such data.

The information provided in this section of the dossier will vary in the level of detail as determined by clinical risk of the product, its technical complexity, its novelty⁵, whether it has been associated with a significant number of adverse events, including use errors, and if it or a similar product is associated with specific public health concerns.

A summary of outcomes should be provided that contains enough information to allow WHO to assess the validity of that information. It should include any references to relevant international or published standards or guidelines that have been applied in the production of the data. It should also include a review of relevant published literature regarding the product or substantially similar products.

Detailed information on each performance claim should be provided and include:

- the complete study protocol
- the method of data analysis
- the complete study report
- the study conclusion.

Actual test result summaries with their acceptance criteria should be provided and not just pass/fail statements.

7.1. Analytical studies

7.1.1. Specimen type

This section should describe the different specimen types that can be used with the product. This should include their stability and storage conditions.

Stability includes storage and, where applicable, transport conditions. Storage includes elements such as duration, temperature limits and freeze/thaw cycles.

This section should include detailed information for each matrix and anticoagulant, when applicable, including a description of the measurement procedure for comparison or determination of measurement accuracy. This includes information such as specimen types tested, number of samples, sample range (using spiked samples, as appropriate) or target concentrations tested, calculations and statistical methods, results and conclusions.

⁵ A product is considered novel if it has any of the following characteristics:

- It incorporates novel technology, which many mean that there is no other similar product on the market for that particular analyte or the procedure involves analytical technology not continuously used in connection with the given analyte or other parameter on the market.
- It is an already marketed product that is now being offered for an intended use different from the original one.
- It incorporates novel or potentially hazardous materials.

7.1.2. Analytical performance characteristics

7.1.2.1. Accuracy of measurement

This section should describe both trueness and precision studies ⁶.

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

7.1.2.1.1. Trueness of measurement

This section should provide information on the trueness of the measurement procedure and summarize the data in sufficient detail to allow assessment of the adequacy of the selected means. Trueness measures apply to both quantitative and qualitative assays only when a reference standard or method is available.

7.1.2.1.2. Precision of measurement

This section should describe repeatability and reproducibility studies.

7.1.2.1.2.1. Repeatability:

This section should include repeatability estimates and information about the studies used to estimate, as appropriate, within-run variability⁷.

Such studies should include the use of samples that represent the full range of expected analyte (measurand) concentrations that can be measured by the product, as claimed by the manufacturer.

For products to be used at point-of-care, where the testing may be undertaken by non-laboratory staff (for example, clinic nurses), it is necessary to establish these specifications using firstly professional laboratory personnel to undertake the tests. This will establish the optimal performance characteristic of the device under controlled laboratory conditions. A consumer field evaluation should also be conducted to determine the product's performance when used by lay users, unassisted, following instructions provided with the product.

⁶ The general term "measurement accuracy" is currently used to cover both trueness and precision, whereas this term was used in the past to cover only the one component now named trueness.

⁷ If a standard recognized by WHO is used, a declaration/certificate of conformity to the recognized standard along with a summary of the data and conclusions should be provided.

7.1.2.1.2.2. Reproducibility:

This section should include reproducibility estimates and information about the studies used to estimate, as appropriate, variability between-days, runs, sites, lots, operators and instruments. Such variability is also known as *intermediate precision*⁸.

Such studies should include the use of samples that represent the full range of expected analyte (measurand) concentrations that can be measured by the product, as claimed by the manufacturer.

For products to be used at point-of-care, where the testing may be undertaken by non-laboratory staff (for example, clinic nurses), it is necessary to establish these specifications using firstly professional laboratory personnel to undertake the tests. This will establish the optimal performance characteristic of the device under controlled laboratory conditions. A consumer field evaluation should also be conducted to determine the product's performance when used by lay users, unassisted, following instructions provided with the product.

7.1.2.2. Analytical sensitivity

This section should include detailed information about the study design and results. It should provide:

- a description of specimen type and preparation including matrix, analyte (measurand) levels, and how levels were established;
- the number of replicates tested at each concentration;
- a description of the calculation used to determine assay sensitivity.

For example:

- The number of standard deviations above the mean value of the sample without analyte (measurand), commonly referred to as *limit of blank (LoB)*.
- The lowest concentration distinguishable from zero, based on measurements of samples containing analyte (measurand), commonly referred to as *limit of detection (LoD)*.
- Lowest concentration at which precision and/or trueness are within specified criteria, commonly referred to as *limit of quantitation (LoQ)*.

7.1.2.3. Analytical specificity

This section should describe interference and cross reactivity studies to determine the analytical specificity, 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 sample.

Provide detailed information on the evaluation of potentially interfering and cross reacting substances/agents on the assay. Information should be provided on:

- the substance/agent type and concentration tested
- sample type

⁸ See footnote 6.

- analyte (measurand) test concentration and
- results.

NOTE: Interferents and cross reacting substances/agents, which vary greatly depending on the assay type and design, could derive from exogenous or endogenous sources such as:

- 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 sample preparation (e.g. preservatives, stabilizers);
- substances encountered in specific specimens 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: test specimens negative for hepatitis A virus, but positive for hepatitis B virus).

Typically, interference studies involve adding the potential interferent to the sample and determining any bias of the test parameter relative to the control sample to which no interferent has been added.

7.1.2.4. Metrological traceability of calibrators and control material values

Detailed information should be provided about the metrological traceability of values assigned to calibrators and trueness control materials. Include, for example, methods and acceptance criteria for the metrological 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 metrological traceability to a reference material or a reference method.

7.1.2.5. Measuring range of the assay

This section should include detailed information on studies which define the measuring range (linear and non-linear measuring systems), including the limit of detection, and describe information on how these were established. This information should include:

- a description of specimen type, number of samples, number of replicates, and preparation;
- information on matrix, analyte (measurand) levels and how levels were established;
- if applicable, a description of high dose hook effect and the data supporting the mitigation (e.g. dilution) steps.

7.1.2.6. Validation of assay cut-off

This section should provide detailed information on analytical data with a description of the study design, including methods for determining the assay cut-off, including:

- the population(s) studied (demographics / selection / inclusion and exclusion criteria / number of individuals included);
- the method or mode of characterization of specimens; and

- the statistical methods e.g. Receiver Operator Characteristic (ROC) to generate results and, if applicable, define gray-zone/equivocal zone.

7.2. Stability (excluding specimen stability)

This section should describe claimed shelf life, in use stability and shipping studies⁹.

Wherever possible, the manufacturer should look to internationally accepted methods for determining stability of diagnostics¹⁰. Where specific standards or guidelines for stability study design and implementation are recommended by WHO, these should be followed.

NOTE: The manufacturer should provide sufficient detail to support stability claims. The provision of stability data alone is not sufficient. The information described above should be provided in a clear manner, such that it can be easily reviewed.

7.2.1. Claimed shelf life

This section should provide detailed information on stability testing studies to support the claimed shelf life. Testing should be performed on **at least three different lots** manufactured under conditions that are essentially equivalent to routine production conditions (these lots do not need to be consecutive lots). Accelerated studies or extrapolated data from real time data are acceptable for initial shelf life claim but need to be followed up with real time stability studies.

Such detailed information on stability testing studies should include:

- the study report (including the protocol, number of lots, acceptance criteria and testing intervals);
- when accelerated studies have been performed in anticipation of the real time studies, the method used for accelerated studies;
- conclusions and claimed shelf life.

NOTE: Shelf life can be derived from the lot with the longest real time stability data as long as accelerated or extrapolated data from all three lots are comparable.

7.2.2. In use stability

This section should provide detailed information on in use stability studies **for one lot** reflecting actual routine use of the device (real or simulated). This may include open vial stability and/or for automated instruments, on board stability.

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

Such detailed information should include:

- the study report (including the protocol, acceptance criteria and testing intervals)

⁹ Shelf-life, in-use stability and shipping stability information provided under this section should be consistent with the instructions for use and product labels provided within the product dossier.

¹⁰ See reference documents under Section 13.

- the conclusion and the claimed in use stability.

7.2.3. Shipping stability

This section should provide detailed information on shipping stability studies **for one lot** to evaluate the tolerance of products to the anticipated shipping conditions.

Shipping studies can be done under real and/or simulated conditions and should include variable shipping conditions such as extreme temperature (heat and/or cold), humidity, light and/or pressure.

Such detailed information should include:

- the study report (including the protocol and acceptance criteria)
- the method used for simulated conditions
- the conclusion and the recommended shipping conditions.

7.3. Software verification and validation

The dossier should contain detailed evidence of the validation of the software, as used in the finished product. This information should typically include the summary results of all verification, validation and testing performed in-house and, as applicable, in an actual user environment prior to final release. It should also address all of the different hardware configurations and, where applicable, operating systems identified in the labelling.

7.4. Clinical evidence (clinical or diagnostic sensitivity and specificity)

Clinical evaluation is the assessment and analysis of data generated from the clinical use of the product in order to verify the clinical safety and performance of the device. Clinical evidence is the combined information yielded by the clinical data and its evaluation. It is necessary for a manufacturer to hold clinical evidence of any clinical claims. This will include claims for clinical or diagnostic sensitivity and specificity.

7.4.1. Clinical evaluation - Manufacturer

All performance claims should be supported by well-designed performance evaluations which have been carried out or coordinated by the manufacturer¹¹. Provide information for these performance evaluations which should include:

- A detailed written plan and protocol which explains the intent of the evaluation study and the way in which the study was performed.
- The date/s on which the study was performed and by which site.
- A written report on the outcome of study. This report should explain how the study results support the product clinical claims. Any anomalous results, or results that are not within predetermined specifications, should be clearly explained or justified.
- Clear identification of the product and product version that is being evaluated.
- Details of the product lots/batches used for the evaluation, including lot number, date of expiry, and the storage conditions of the product prior to and during the study.

¹¹ The Common Technical Specifications for in vitro diagnostic medical devices (2009/886/EC) of the European Communities can be considered a guide for establishing clinical specifications. However, the clinical evaluation should utilize samples obtained from populations equivalent to where this product will be supplied.

- Details of the geographical region and the clinical status of the subjects from which specimens have been drawn for the clinical evaluation.
- Full details of the methods used to define the clinical status of the subjects and to characterize the specimens.
- Full details of statistical methods, estimations and calculations applied.
- Evidence that the outcomes of the performance studies have been reviewed and accepted for implementation.

NOTE: Actual test results and their acceptance criteria should be provided, and not just pass/fail statements. All data provided should be clearly labeled, and should be clearly linked to the study report. Furthermore, all abbreviations used in reports and on data records should be defined and spelt out in full.

7.4.2. Clinical evaluation - Independent study

Details of at least one well-designed independent performance evaluation for the product under assessment should be included. Only include information from independent performance evaluations that have been carried out by centres that have the capability of performing scientifically sound evaluation studies for the product in question.

Scientifically sound performance evaluations should include:

- the evaluation study design, study protocol, results, and conclusions;
- the date/s on which the study was performed;
- clear identification of the product and product version that is being evaluated;
- details of the product lots/batches used for the evaluation, including lot number, date of expiry, and the storage conditions of the product prior to and during the study;
- details of the geographical region and the clinical status of the subjects from which specimens have been drawn for the clinical evaluation;
- details of the methods used to define the clinical status of the subjects and to characterize the specimens;
- details of statistical methods, estimations and calculations applied;
- details of the entity which performed the evaluation, including current contact details;
- a declaration from the entity which performed the evaluation declaring any interests that could constitute a real, potential, or apparent conflict of interest with respect to their involvement in the independent evaluation of this product or the manufacturer of the product.

If the study has been published in peer-reviewed scientific literature, provide publication details for the study.

NOTE: Testimonials from hospitals, laboratory staff, product users, patients, or testimonials of any other kind are not considered to be evidence of performance. Testimonials should not be included in the dossier as they will not be considered during review.

8. Labelling

The product dossier should typically contain a complete set of labelling associated with the product. Information on labelling should include the following:

- packaging labels
- instructions for use
- if applicable, the instrument manual
- any other instructional materials provided to the user.

8.1. Labels

Include copies of all the packaging labels for the assay - include outer package labels and also component labels. These labels should include at a minimum of information:

- the product name and product identification 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;
- an indication of any special storage and/or handling conditions that apply;
- the warnings and precautions;
- the lot/batch and/or serial number;
- the information regarding particular product conditions such as product sterility;
- the names of all included reagents in each box on the outer package label.

If the product requires associated instrumentation, the above requirements also apply to the instrument. In addition, the instrument should clearly display information regarding its status as a new or reprocessed product.

8.2. Instructions for use

A copy of the current instructions for use should be included. If at the application form stage the manufacturer has been required to address any issues related to the instructions for use, the amended instructions for use should be submitted as part of the dossier. The instructions for use will be reviewed for clarity, correctness, and suitability for the target user group. The instructions for use should at a minimum include the following information¹²:

1. The product name and product identification number.
2. The name and contact details of the manufacturer or an authorized representative of the manufacturer, in order for the user to obtain assistance.
3. The intended use, including:
 - a) what is detected by the assay (that is, the analytical use of the assay e.g. the marker or nucleic acid sequence being detected);
 - b) 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);
 - c) the function of the product (screening, monitoring, diagnostic or aid to diagnosis,

¹² Labelling requirements that apply to the WHO prequalification of diagnostics programme are based on the document GHTF/SG1/N43:2005 Labeling for Medical Devices.
PQDx_018 v1 06.05.2010

- staging or aid to staging of disease);
 - d) the intended user (laboratory professional and/or at point-of-care);
 - e) the intended testing population (e.g. neonates, antenatal women);
 - f) the type of specimen(s) required (e.g. serum, plasma, whole blood, sputum, urine).
 - g) whether the assay is automated;
 - h) what the instrument is intended for;
 - i) whether the test is qualitative or quantitative;
 - j) an indication that the product is for in vitro use.
4. A general description of the principle of the assay method or instrument principles of operation.
 5. 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.).
 6. A description of the specimen collection and transport materials provided with the product or recommended for use.
 7. For instruments of automated assays: a description of the appropriate assay characteristics or dedicated assays.
 8. For automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation.
 9. If applicable, a description of any software to be used with the product.
 10. If applicable, a description or complete list of the various configurations/variants of product that will be made available.
 11. If applicable, a description of the accessories, and other products that are intended to be used in combination with the product.
 12. 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.
 13. Specimen exclusion criteria e.g. samples with visual evidence of hyperlipidaemia or haemolysis, excessive sample age, excessive number of freeze/thaw cycles.
 14. If the test kit includes sterile accessories, an indication of that condition and any necessary instructions in the event of damage to sterile packaging.
 15. If the test kit includes accessories that have been specified by the manufacturer as intended for single-use only, an indication of that state.
 16. 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 and the interpretation of results.
 17. Recommendations for quality control procedures.
 18. Clear instructions on the correct usage of any equipment or software that is required for the performance of the assay.
 19. 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) or to any potentially infectious substances of human or animal origin.

20. Any residual risks¹³.
21. Precautions and measures to be taken in the event of performance changes or product malfunction.
22. Limitations of the assay, including information on interfering substances that may affect the performance of the assay.
23. Performance characteristics such as clinical sensitivity and specificity, seroconversion sensitivity, accuracy, dynamic range, lower limit of detection, reproducibility, and any other performance aspects that are relevant to the product.
24. Any requirements for special training or particular qualifications of the assay user.
25. 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).
26. Document control details, such as a document version number and release date.

If the product requires associated instrumentation, also include a copy of the instrument manual. If the instrument manual is large, an electronic version (CD or DVD) may be included instead of a hard-copy.

Provide copies of any other instructional materials that are provided to the user.

9. Commercial History

9.1. Countries of supply

The information provided in this section should include:

- A list all countries in which the product under assessment is currently supplied and the year when supply started. This includes all countries where the diagnostic has been made available, in return for payment or free-of-charge, for distribution and/or use in that country.
- Detailed information about the training and support network that is available in each country of supply. For example:
 - a) how the users are trained in the operation of the assay;
 - b) how the users of the product contact the supplier/manufacturer for technical support;
 - c) if there are representatives located in each country of supply to provide technical support; and
 - d) how many representatives are available in each country of supply to provide technical support.
- The minimum and maximum price of supply for this product for the last financial year. These prices should be the global minimum and maximum prices and should be quoted in US dollars.

9.2. Adverse events and field safety corrective actions

This section should provide the following information:

¹³ For more information see ISO 14971:2007 Medical devices - Application of risk management to medical devices.

- A list of all adverse events that have occurred (within the last five years) that did affect, or could have potentially affected, the performance of the assay, safety of the person being tested, safety of users of this test, or safety of any person associated with this product. Include details of the corrective and preventative action taken.
- A list of all events (within the last five years) that required field safety corrective action such as:
 - a) withdrawal of products from sale or distribution
 - b) physical return of the product to the manufacturer
 - c) product exchange
 - d) destruction of the product
 - e) product modification/s
 - f) additional advice provision to customers to ensure that the product continues to function as intended.

10. Regulatory History

A "National Regulatory Authority" (sometimes also called a Competent Authority) is an entity that exercises the legal right to act on behalf of the Government of a country/region to control the use and supply of diagnostics in that country/region.

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

"Type of regulatory approval" refers to the relevant sections of 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.

For the diagnostic under assessment include:

- A list of National Regulatory Authorities which have provided current regulatory approval for the supply of this product in their country/region of authority.
- Details of the type of regulatory approval obtained from each National Regulatory Authority (this refers to the relevant sections of the legislation that have been applied to the product for regulatory approval).
- Current evidence of this 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.
- Details regarding any situations where this product was rejected by a National Regulatory Authority, situations where an application for regulatory approval was withdrawn, or situations where regulatory approval has been withdrawn.

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

11. Quality Management System

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

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

11.1. Quality manual

Include a copy of the current version of the manufacturer's quality manual¹⁴. The following aspects should be covered (or referred to) in the quality manual¹⁵:

- the title and scope
- the table of contents
- the review, approval and revision
- the quality policy and objectives
- the organization, responsibility and authority
- the references
- The quality management system description and
- The appendices.

Include the organizational chart of the manufacturer (if not already available within the quality manual) and document control information for the quality manual (such as version number, release date and approval record).

A complete list of all quality management system documents, with the document title and document number, relevant to this product should be included.

11.2. Quality management system documents

It is expected that, to maintain an effective quality management system for the manufacture of this diagnostic, the manufacturer will utilize a number of documented procedures. Provide copies of the following documented procedures applied in the manufacture of this diagnostic:

- The manufacturer's documented procedure/s, relevant to this product, for the control of design and development changes.

¹⁴ The manufacturer's quality manual is expected not to exceed 30 pages. However, if it does, please provide only the electronic copy (CD or DVD) of the document.

¹⁵ These requirements are based on the ISO/TR 10013:2001 Guidelines for quality management system documentation. For further information see the following website: www.iso.org

- The manufacturer's documented procedure/s, relevant to this product, for the provision of advisory notices to customers subsequent to product delivery.
- The manufacturer's documented procedure/s for corrective and preventative actions for non-conformities relating to the product under assessment.

11.3. Quality management system certification

If the manufacturer holds *ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes* certification for the manufacture of the product under assessment, then provide evidence, such as certified copies of the certificates issued by the Conformity Assessment Body. Ensure that any certificates provided clearly demonstrate that the manufacture of the product under assessment is within the scope of the certification.

12. Contact Information

Any inquiries regarding the prequalification of diagnostics should be addressed to:

diagnostics@who.int

13. Reference Documents

- ISO 13485:2003 *Medical devices - Quality management systems - Requirements for regulatory purposes* [International Organization for Standardization (ISO) document; www.iso.org]
- ISO/TR 10013:2001 *Guidelines for quality management system documentation* [International Organization for Standardization (ISO) document; www.iso.org]
- ISO 18113 *Clinical laboratory testing and in vitro diagnostic test systems - In vitro diagnostic medical devices - Information supplied by the manufacturer (labeling) - Part 1 - 5*
- ISO/TR 18112:2006 *In vitro diagnostic medical devices for professional use - Summary of regulatory requirements for information supplied by the manufacturer*
- ISO15198:2004 *Clinical laboratory medicine - In vitro diagnostic medical devices - Validation of user quality control procedures by the manufacturer*
- ISO 17511:2003 *Metrological traceability of values assigned to calibrators and control materials*
- ISO 14971:2007 *Medical devices - Application of risk management to medical devices*
- EN 13641:2002 *Elimination or reduction of risk of infection related to in-vitro diagnostic reagents*

- EN 13612:2002 Performance evaluation of in vitro diagnostic medical devices
- EN 13640:2002-06 *Stability testing of in vitro diagnostic reagents* [European Committee for Standardization (CEN) document www.cen.eu]
- GHTF/SG1/N41R9:2005 *Essential Principles of Safety and Performance of Medical Devices* [Global Harmonization Task Force (GHTF) document; www.ghtf.org]
- GHTF/SG1/N43:2005 *Labelling for Medical Devices* [Global Harmonization Task Force (GHTF) document; www.ghtf.org]
- GHTF/SG2/N54R8:2006 *Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices* [Global Harmonization Task Force (GHTF) document; www.ghtf.org]
- GHTF/SG2/N57R8:2006 *Medical Devices Post Market Surveillance: Content of Field Safety Notices* [Global Harmonization Task Force (GHTF) document; www.ghtf.org]
- CLSI EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline (2009)

14. Annex A - Essential Principles (EP) checklist

The EP checklist can be used by manufacturers to readily understand how the manufacturer demonstrates compliance to the Essential Principles for a particular diagnostic. The EP checklist also allows easy identification of relevant documents and data for conformity assessment purposes.

The contents of the checklist vary among diagnostics. More complex diagnostics are more likely to reference a larger number of standards, test reports and documents. The EP checklist in those cases might be many pages long.

The following is a recommended template for the EP checklist. Preparation of the EP checklist as outlined below will provide a useful overview of the manufacturer's conformity to the Essential Principles.

14.1. How to fill in the checklist

14.1.1. Identity of the diagnostic

The manufacturer should identify the diagnostic, and when applicable the various configurations/variants covered by the checklist.

14.1.2. Applicable to device?

Is the listed Essential Principle applicable to the diagnostic? Here the answer is either 'Yes' or 'No'. If the answer is 'No' this should be briefly explained.

14.1.3. Method used to demonstrate conformity

In this column, the manufacturer should state the type(s) of method(s) that it has chosen to demonstrate conformity e.g. the recognised standard(s), industry or in-house test method(s), comparison study(ies) or other method used.

14.1.4. Method reference

After having stated the method in the previous column, here the manufacturer should name the title and reference the recognised standard(s), industry or in-house test method(s), comparison study(ies) or other method used to demonstrate conformity. For standards, this should include the date of the standard and where appropriate, the clause(s) that demonstrates conformity with the relevant EP.

14.1.5. Reference to Supporting controlled documents

This column should contain the reference to the actual technical documentation that demonstrates conformity to the Essential Principle, i.e. the certificates, test reports, study reports or other documents that resulted from the method used to demonstrate conformity and its location within the STED.

NOTE: The table that follows is for illustrative purposes only. The Essential Principles listed in the first column should be extracted from the latest version of the GHTF's guidance document *Essential principles of Safety and Performance of Medical Devices*". Those incorporated into this document are extracted from GHTF/SG1/N41:2005.

Essential Principles Checklist

Identity of the diagnostic:

Essential Principle	Applicable to the device?	Method Used to Demonstrate Conformity	Method Reference	Reference to Supporting Controlled Documents
General Requirements				
<p>5.1 Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.</p>				
<p>5.2 The solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, the manufacturer should control the risk(s) so that the residual risk(s) associated with each hazard is judged acceptable. The manufacturer should apply the following principles in the priority order listed:</p> <ul style="list-style-type: none"> ▪ identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse, ▪ eliminate risks as far as reasonably practicable through inherently safe design and manufacture, ▪ reduce as far as is reasonably practicable the remaining risks by taking adequate protection measures, including alarms, ▪ inform users of any residual risks. 				

Essential Principle	Applicable to the device?	Method Used to Demonstrate Conformity	Method Reference	Reference to Supporting Controlled Documents
5.3 Devices should achieve the performance intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions within the scope of the definition of a medical device applicable in each jurisdiction.				
5.4 The characteristics and performances referred to in Clauses 5.1, 5.2 and 5.3 should not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.				
5.5 The devices should be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected under transport and storage conditions (for example, fluctuations of temperature and humidity) taking account of the instructions and information provided by the manufacturer.				
5.6 The benefits must be determined to outweigh any undesirable side effects for the performances intended.				
Design and Manufacturing Requirements				
5.7 Chemical, physical and biological properties				

Essential Principle	Applicable to the device?	Method Used to Demonstrate Conformity	Method Reference	Reference to Supporting Controlled Documents
<p>5.7.1 The devices should be designed and manufactured in such a way as to ensure the characteristics and performance referred to in Clauses 5.1 to 5.6 of the 'General Requirements'. Particular attention should be paid to:</p> <ul style="list-style-type: none"> ▪ the choice of materials used, particularly as regards toxicity and, where appropriate, flammability, ▪ the compatibility between the materials used and biological tissues, cells, body fluids, and specimens, taking account of the intended purpose of the device, ▪ the choice of materials used should reflect, where appropriate, matters such as hardness, wear and fatigue strength. 				
<p>5.7.2 The devices should be designed, manufactured and packed in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to patients, taking account of the intended purpose of the product. Particular attention should be paid to tissues exposed and to the duration and frequency of exposure.</p>				
<p>5.7.3 ----- etc. -----</p>				
<p>5.7.4 ----- etc. -----</p>				
<p>5.7.5</p>				
<p>5.7.6</p>				