



INSTRUCTIONS FOR COMPILATION OF A PRODUCT DOSSIER

Prequalification of In Vitro Diagnostics Programme

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1. Introduction

The World Health Organization (WHO) Prequalification of In Vitro Diagnostics (IVDs) Programme is coordinated through the department of Essential Medicines and Health Products. The aim of the WHO Prequalification of IVDs Programme is to promote and facilitate access to safe, appropriate and affordable in vitro diagnostics of good quality in an equitable manner. Focus is placed on in vitro diagnostics for priority diseases and their suitability for use in resource-limited settings.

The WHO Prequalification of IVDs Programme undertakes a comprehensive assessment of individual in vitro diagnostics through a standardized procedure aimed at determining if the product meets WHO prequalification requirements. The prequalification assessment process includes three components:

- Review of a product dossier
- Laboratory evaluation of performance and operational characteristics
- Manufacturing site(s) inspection

Post-market surveillance is a WHO post-qualification activity which includes reactive and proactive measures, through complaint reporting and post-shipment/pre-distribution lot testing. Post-qualification also includes mandatory manufacturer notification of changes to the product or the quality management system.

The findings of the WHO Prequalification of IVDs Programme are used to provide independent technical information on safety, quality and performance of IVDs, principally to other United Nations (UN) agencies but also to WHO Member States and other interested organizations. The WHO prequalification status, in conjunction with other procurement criteria, is used by UN agencies, WHO Member States and other interested organizations to guide their procurement of IVDs. Prequalification does not imply any approval by WHO of the product and manufacturing site(s). Moreover, prequalification does not constitute any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety, quality or performance.

2. Intended Audience

This document has been prepared to assist manufacturers in correctly compiling a product dossier for the purposes of WHO prequalification assessment of IVDs, and describes the required product dossier information to support WHO Prequalification of IVDs. This document should be used together with WHO Document PQDx_049 “Product Dossier Checklist”¹. Manufacturers² who wish to submit a product dossier for an IVD should read both of these documents carefully to compile a successful product dossier.

¹ This document may be accessed through the following website:
http://www.who.int/diagnostics_laboratory/evaluations/PQDxInfo/en/index.html

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 IVDs, WHO uses the term the *product dossier*.

WHO expects the manufacturer to prepare and either hold, or provide timely access to, technical documentation that shows how the IVD is developed, designed, 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 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 IVD conforms to the internationally recognized set of safety and performance principles as described in the Global Harmonization Task Force document GHTF/SG1/N68:2012 "Essential Principles of Safety and Performance of Medical Devices".³ Forthwith, these will be referred to as the *Essential Principles*.

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

² For the purposes of the Prequalification of In Vitro Diagnostics Programme, 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)".

³ The Global Harmonization Task Force document GHTF/SG1/N68:2012 "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.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n68-2012-safety-performance-medical-devices-121102.pdf>

3.2. Submission of a Product Dossier

Manufacturers should first follow the instructions in WHO document PQDx_007 “Overview of the Prequalification of In Vitro Diagnostics Assessment”, to have an understanding of the processes that must first be undertaken before a product dossier is submitted.

Note: Manufacturers should not submit a product dossier to WHO unless requested to do so by the Prequalification Team – Diagnostics, as outlined in PQDx_007. Dossiers that are submitted without a request from the WHO will be destroyed without review.

3.3. Product Dossier clarity

Manufacturers should make every effort to ensure that their product dossier is clear and well-organized to help make the prequalification assessment procedure as efficient as possible.

Note: Poorly prepared dossiers may be rejected and destroyed without full review.

3.4. Product Dossier completeness

Manufacturers must submit all necessary sections of a product dossier, identified both in this document and in WHO Document PQDx_049 “Product Dossier Checklist”.

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

3.5. Product Dossier content and the Pre-submission Form

Information that was previously submitted in the “Pre-Submission Form” WHO 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 pre-submission form and that any changes in the information submitted with the respective pre-submission form are promptly notified to WHO.

Furthermore, inadequacies identified at the pre-submission form stage and communicated by WHO to the manufacturer are expected to be addressed as part of the product dossier submission.

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

3.6. Product Dossier Requirements – Important guidance on documents to be submitted

Note: All items preceded by the symbol “➤” in each section below are required to be submitted as part of the product dossier (or, when indicated, as applicable). These items also appear in the dossier submission checklist, which is used by WHO to assess dossier completeness.

4. Dossier Format

4.1. Product Dossier submission format

- Submit one printed copy and one electronic copy (exact duplicate of the printed copy in a CD or DVD only) of the entire product dossier. Submit a signed document attesting that the content of the electronic version is an exact duplicate of the printed copy.
- Provide the printed product dossier either bound or in a clearly marked set of ring-binders.

Note: The printed copy will be destroyed by WHO after completion of the dossier screening phase.

4.2. Layout and order

WHO requires the following format for the dossier submission:

- Use the format *1 of 2, 2 of 2*, etc.
- Clearly divide the submission into sections, as prescribed in the WHO document PQDx_049 “Product Dossier Checklist”, and number all pages of each section so that they are easily identified.
- Include a table of contents.
- Use the Product Dossier Checklist (document PQDx_049) as the first page, and cross-reference all sections of the dossier to this first page.
- The physical pages of the dossier and the page numbers should correspond.
- Ensure that there are appropriately named tab identifiers. The names should link directly with the sections of the dossier as outlined in this WHO document PQDx_018 “Instructions for Compilation of a Product Dossier”. For example, the Labelling information should be separated from the other documents by a tab identifier named “Section 8.1 Labels”.
- Standard A4 paper is used for all submissions. Text and tables should be prepared using margins that allow the document to be printed on A4 paper. The left hand margin should be sufficiently large that information is not obscured through binding.
- Font sizes for text and tables are of a style and size that are large enough to be easily legible, even after photocopying or when provided electronically. Fonts smaller than 12 points should be avoided whenever possible, except in tables and footnotes where a font size of 10 points is acceptable.

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 supplied.
- the information is fully cross-referenced to the WHO Prequalification of IVD Programme requirements using the “Product Dossier Checklist”, WHO document PQDx_049.

Manufacturers should contact WHO regarding to determine if a particular prior regulatory authority submission is appropriate to substitute for the dossier.

4.2.1 Electronic copy requirements

- PDF is the primary file format used for the electronic copy. However, you must not include any PDF that requires a password to open it.
- The electronic copy must be organized as per the format prescribed for the printed copy.
- The name of the file name should be descriptive of its content and meaningful to the reviewers. The name can be up to 125 characters and can have spaces, dashes (not elongated dashes), underscores, and periods. However, the name of the file must not contain any of the following special characters or it will fail the loading process:
 - tilde (~)
 - vertical bar (|)
 - asterisk (*)
 - forward slash (/)
 - elongated dash (–)
 - backward slash (\)
 - apostrophe (')
 - greater than sign (>)
 - single quotation mark (')
 - less than sign (<)
 - double quotation marks (“ ”)
 - question mark (?)
 - colon (:)
 - various other symbols (e.g., \rightarrow , $*$, β , α , ∞ , \pm , $^{\text{TM}}$)
 - pound sign (#)
- When creating a PDF from the source document (e.g. Microsoft Word document), please consider when using Adobe® plug-ins to create PDF files and/or capture or display data, there is a risk that information may not display correctly because reviewers may not have access to certain plug-ins to review content being displayed by a plug-in.
- All PDF files should be created directly from the source documents whenever feasible rather than creating them by scanning. PDF documents produced by scanning paper documents are far inferior to those produced directly from the source document, such as a Microsoft Word document, and, thus, should be avoided if at all possible. Scanned documents, particularly tables and graphs, are more difficult to read. For any scanned document, we highly recommend that you perform optical character recognition (OCR) so that the text is searchable. Check to see that the content has been correctly converted by: (1) highlighting an area of text and (2) searching for a word or phrase. If the word or phrase is not returned in the search, then the OCR did not recognize the text. WHO recognizes that use of OCR may not be feasible in some cases for documents with figures and images. Hence, there may be cases in which it is appropriate to have scanned documents in the electronic copy.

4.3. Language and units of measurement

For the purposes of Prequalification of IVDs, the following requirements apply:

- Submit all documents presented in the dossier in English (unless other arrangements have been made with WHO **prior to** submission of the dossier).
- Any translations of documents must be carried out by a certified translator. Provide an official document attesting to the accuracy of the translation and details on the credentials of the translator. Provide both the original and the translated documents.
- All measurements units used must be expressed in the International System of Units (SI).

5. Product Information

5.1. Regulatory versions of this product

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 prequalification.

- 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.**
- Ensure that for any of the documents submitted in the product dossier, that the regulatory version to which it relates is identified. Where it is not the version submitted for prequalification, a justification for its inclusion in the product dossier should be provided.

5.2. Product description including variants (configurations) and accessories

The dossier should include product descriptive information sufficient to allow the dossier assessor to understand the product and how it functions. 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. Provide the following information:

- The intended use of the diagnostic.
 - What the product detects.
 - The function of the product (e.g., screening, monitoring, diagnostic or aid to diagnosis, staging or aid to staging of disease).
 - The specific disorder, condition or risk factor of interest that the product is intended to detect, define or differentiate.
 - Whether the product is automated or manually operated.
 - Whether the test is qualitative or quantitative.

- The type of specimen(s) required (e.g. serum, plasma, whole blood, sputum, urine, etc.).
- The intended testing population (e.g. neonates, antenatal women, symptomatic individuals, etc.).
- The intended user (laboratory professional and/or health care worker at point-of-care).
- The intended setting of use (laboratory, point-of-care).
- Photographs of all kit components (packaged and individually).
- A general description of the principle of the assay method or instrument principles of operation.
- 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).
- A description of the specimen collection and transport materials are provided with the product or descriptions of specifications 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 diagnostic.

5.3. Essential Principles Checklist

The product dossier will provide evidence of conformity to the “Essential Principles” as outlined in document GHTF/SG1/N68:2012 “Essential Principles of Safety and Performance of Medical Devices-November 2012” (<http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n68-2012-safety-performance-medical-devices-121102.pdf>). The Essential Principles that apply to IVDs will be found in sections 5, 6, and 8 of the GHTF document.

- Include in the dossier an Essential Principles checklist in the form of a table that lists:
 - The Essential Principles of Safety and Performance applicable to IVDs (all Essential Principles from sections 5, 6 and 8 of the GHTF document).
 - Whether each Essential Principle applies to the IVD for prequalification and if not, provide a justification as to why not.
 - The method used to demonstrate conformity with each Essential Principle that applies, as well as the reference for the method used.
 - A reference for the manufacturer’s actual technical documentation that provides evidence of conformity with each method used.

- Where that technical documentation is located, both within the full technical documentation held by the manufacturer (e.g., the names of documents) and within the dossier (when such documentation is specifically required for inclusion in the dossier as outlined in this instructions).

Note: Annex A contains additional information on the Essential Principles checklist, as well as a sample. Note that this table does not show a complete list of Essential Principles for IVDs, but is meant to serve as an example. The manufacturer should provide a complete table extracted from the GHTF document listed above that addresses all of the Essential Principles applicable to IVDs.

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 product dossier should 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
 - User-related hazards, such as reagents containing infectious agents
 - Production-related risks
- A description of how these risks have been controlled to an acceptable level.
- A conclusion with evidence that the remaining risks are acceptable when compared to the benefits. This should be signed by senior management.
- Evidence that the risk analysis is part of the manufacturer's risk management plan (inclusion of the relevant manufacturer's document).
- Identification of specific standards or guidelines recommended by WHO, when applicable (for example, ISO 14791:2007 (E) "Medical devices -- Application of risk management to medical devices").

6. Design and Manufacturing Information

This section of the dossier provides information on the design and manufacturing processes for the product under assessment.

⁴ Examples of possible hazards and contributing factors associated with IVDs are given in ISO 14971:2007 (E) Annex H.

6.1. Product design

6.1.1. Design overview

- Provide information to allow a reviewer to obtain a general understanding of the design applied to the product. A schematic presentation can assist.
- **Provide a flowchart of the design process including design inputs and outputs for the product for prequalification.**
- Provide a general 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, identify a controlling site.

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 IVD components are constructed.

6.1.3. Biological safety

- Provide a table or list of 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 table or list should include:
 - the name of the biological component
 - details of the use of the biological component in the product
 - a description of steps taken for the reduction of transmission or infection risk
- 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. If there are no such methods that apply to the product, state that this is the case
- Provide information on how users of the device are informed of any residual risk

6.1.4. Documentation of design changes

- Provide records of each design change for the product submitted for prequalification, including:
 - The reasons that each change was made
 - References to validation/verification data to support the change
 - Evidence 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 sufficient 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 that is required for a QMS audit or other conformity assessment activity.

- Provide a flow chart of the entire manufacturing process. If design and manufacture is carried out at different sites, or by external suppliers, this should be indicated on the flow chart. Only refer to sites of suppliers of raw materials involved in critical design and manufacturing activities.
- Provide a site master file, including a diagram of the floor plan.
- If Quality Management System certificates, or the equivalent, exist for any sites, annex certified copies to the dossier. If no such certificates exist, state this.
- 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 process flow charts (in addition to the general manufacturing 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.
- Provide 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).
- Provide the batch release criteria for this product.

6.2.2. Sites of manufacture

- Provide a list of all critical manufacturing sites that are involved in the manufacture of this product.
- 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 facilities that have been presented in the product dossier will be considered to be prequalified. WHO must be notified of any changes to manufacturing facilities **prior to** implementation of the changes.

6.2.3. Key suppliers

- List all key suppliers of 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 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.

Note: WHO should be notified of all variations/changes made to a prequalified product. This includes changes of key suppliers and components/products/services provided by key suppliers. Refer to WHO document PQDx_121 "WHO Procedure for Changes to a Prequalified In Vitro Diagnostic".

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

The manufacturer must 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. 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 take into account the intended user and the intended setting of use.

- **For each study to be submitted, the following must be provided:**
 - Study description, study identifier, product identifier (for example, lot numbers), IFU version used, the date of initiation and the date of completion
 - A summary of the study findings including a conclusion that clarifies how the study objectives have been met

- The study protocol and full report, which incorporates at a minimum, the following information:
 - study objectives, study design, the methodology used and data collected
 - the site where the study was performed (for example, Manufacturers R&D laboratory, hospital laboratory, health care clinic)
 - operator of the assay
 - the reference standard, if applicable
 - specimen acceptance criteria, specimen characterisation
 - specimen type (serum, plasma, finger stick whole blood, venous whole blood) and numbers of each type
 - actual test result summaries with their acceptance criteria and not just pass/fail statements
 - all data is clearly labeled, and clearly linked to the study report
 - details of statistical methods, estimations and calculations applied
 - the study conclusion
 - when performed by a party other than the manufacturer, details of this party and the relationship to the manufacturer

7.1. Analytical studies

7.1.1. Specimen type

This section contains information on the types of specimens that can be used with the IVD.

- Identify the different specimen types that can be used with the product, including:
 - detailed information for each matrix and anticoagulant, when applicable
- Provide the studies and the information identified in the introduction to Section 7 supporting the use of each specimen type (and where applicable, anticoagulant).
- Provide the studies and the information identified in the introduction to Section 7 in support of stability claims, storage claims and, where applicable, claims for transport conditions for each applicable specimen type, including:
 - duration
 - temperatures
 - number of allowable freeze/thaw cycles
 - specimen stability claims

7.1.2. Analytical performance characteristics

7.1.2.1. Accuracy of measurement

This section describes both trueness and precision studies.⁵

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

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

- Provide the studies and the information identified in the introduction to Section 7 to establish trueness providing sufficient detail to allow assessment of the adequacy of the selected means.

7.1.2.1.2. Precision of measurement

This section describes repeatability and reproducibility studies.

7.1.2.1.2.1. Repeatability

This section includes repeatability estimates and information about the studies used to estimate, as appropriate, within-run variability.

- Provide the studies and the information identified in the introduction to Section 7 to establish within-run variability. Such studies should include the use of specimens 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 trained personnel (for example, clinic nurses), repeatability should be established in two steps, first, with professional laboratory personnel to establish the optimal repeatability of the IVD under controlled laboratory conditions then followed by a consumer field evaluation to determine the product's performance when used by non-laboratory trained personnel, unassisted, following instructions provided with the product.

⁵ 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.

- If the IVD is intended for use at the point-of-care, include studies to establish repeatability undertaken by non-laboratory trained personnel representative of expected end users in a WHO setting, who have undertaken the testing unassisted, following instructions provided with the product.

7.1.2.1.2.2. *Reproducibility*

This section contains 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*.

- Provide the studies and the information identified in the introduction to Section 7 to establish as appropriate:
 - inter-day variability
 - inter-run variability
 - inter-site variability
 - inter-lot variability
 - inter-operator variability
 - inter-instrument variability
- Include the use of specimens 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 trained personnel (for example, clinic nurses), repeatability should be established in two steps, first, with professional laboratory personnel to establish the optimal repeatability of the IVD under controlled laboratory conditions then followed by a consumer field evaluation to determine the product's performance when used by non-laboratory trained personnel, unassisted, following instructions provided with the product.

- If the IVD is intended for use at the point-of-care, provide studies to establish reproducibility undertaken by non-laboratory trained personnel representative of expected end users in a WHO setting, who have undertaken the testing unassisted, following instructions provided with the product.

7.1.2.2. *Analytical sensitivity*

This section includes detailed information about the study design and results to determine the analytical sensitivity of the IVD.

- Provide the studies and the information identified in the introduction to Section 7 to establish analytical sensitivity and include:
 - 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 a quantitative assay**, identify the following parameters and provide details on 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

7.1.2.3. Analytical specificity

This section describes 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 specimen. Where possible, studies should address the influence of substances or agents that could be expected to be encountered in the setting of intended use. For WHO purposes, this would include consideration of other common infectious agents and related treatments for patients in resource limited settings in WHO Member States including those in Africa and Asia.

- Provide the studies and information identified in the introduction to Section 7 to evaluate the effects of potentially interfering and cross-reacting substances/agents on the assay. Include:
 - the substance/agent type and concentration tested
 - specimen type
 - analyte (measurand) test concentration
 - a study design that includes appropriate interferents and cross-reacting substances/agents. These will vary depending on the assay type and design, and could derive from exogenous or endogenous sources. Typically, interference studies involve adding the potential interferent to the specimen and determining any bias of the test parameter relative to the control specimen to which no interferent has been added. Common interferents and cross-reacting substances/agents 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 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)
- Interference and cross-reactivity should be evaluated for their potential to cause false positive results (using specimens that do not contain the analyte) and to cause false negative results (using specimens with the analyte added to a low level of reactivity on the IVD)

7.1.2.4. Traceability of calibrators and control material values

- Provide detailed information about the traceability of values assigned to calibrators and trueness control materials supplied with the assay (if applicable) and also 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.

7.1.2.5. Measuring range of the assay

This section provides information on studies that define the measuring range of the assay (linear and non-linear measuring systems), including the limit of detection, and describes information on how they were established.

- Provide the studies and the information identified in the introduction to Section 7 and include:
 - a description of specimen type, number of specimens, number of replicates, and the method of specimen 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 provides information on how the assay cut-off is determined.

- Provide the studies and the information identified in the introduction to Section 7 and include:
 - analytical data with a description of the study design, including methods for determining the assay cut-off

- the population(s) studied (demographics/selection/inclusion and exclusion criteria/number of individuals included)
- the method or mode of characterization of specimens
- the statistical methods (e.g., Receiver Operator Characteristic [ROC]) to generate results and, if applicable, define a gray-zone/equivocal zone

7.1.2.7. Validation of assay procedure – reading time

This section provides information on how the reading time (either end point or reading window) claimed in the Instructions for Use was determined.

- Provide the studies and the information identified in the introduction to Section 7.

7.2. Stability (excluding specimen stability)

This section describes claimed shelf life of the IVD, in-use stability and shipping studies.⁶

- Provide the studies and the information identified in the introduction to Section 7.
- Wherever possible, the manufacturer should look to internationally accepted methods for determining stability of diagnostics.⁷ Where specific standards or guidelines for stability study design and implementation are recommended by WHO, these should be followed.

7.2.1. Claimed shelf life

This section provides information on stability testing studies to support the claimed shelf life.

- Provide the information identified in the introduction to Section 7, ensuring that testing is done on **at least three different lots** manufactured under conditions that are equivalent to routine production conditions (these lots do not need to be consecutive lots).
- The study protocol must specify acceptance criteria and testing intervals.
- 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**. Results derived from testing three different lots is required.
- When accelerated studies have been performed in anticipation of the real time studies, identify the method used for accelerated studies.
- Ensure that the shelf life is derived from the lot with the shortest real time stability data (as long as accelerated or extrapolated data from all three lots are comparable).
- The conclusions must clearly identify claimed shelf life stability.

⁶ Shelf-life, in-use stability and shipping stability information provided under this section must be consistent with the instructions for use and product labels provided within the product dossier.

⁷ See reference documents under Section 13.

7.2.2. *In-use stability*

This section provides information on the in-use stability for the IVD. Studies should be submitted for each assay component.

- Provide the studies and the information identified in the introduction to Section 7, for each assay component (for example, test cartridge, buffer, conjugate, substrate, acid).
- For each component, testing is required on a minimum of **one lot**.
- The studies should reflect actual routine use of the device (real or simulated). This would include open vial stability and/or, for automated instruments, on-board stability. Consideration should be given to multiple access of reagent bottles (opened several times during its use).
- The study protocol must specify acceptance criteria and testing intervals.
- In the case of automated instrumentation, if calibration stability is claimed, then supporting data should be included.
- The conclusions must clearly identify the claimed in-use stability.

7.2.3. *Shipping stability*

This section provides information on shipping stability studies.

- Provide the information identified in the introduction to Section 7, from studies of **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.
- These studies must reflect the environmental conditions of the countries of supply. The information provided must include a justification for the anticipated conditions.
- The study protocol must specify acceptance criteria and testing intervals.
- If simulated conditions are used, the methods used must be identified.
- The results and conclusions must clearly demonstrate that the product will be effective at the end of its claimed shelf life after being subjected to the anticipated shipping conditions. As such, it is necessary that after the product has been subjected to the stressed conditions, that there is testing at the end of the claimed shelf life to demonstrate stability.

7.3. Robustness Studies

This section provides information to demonstrate that the product design is robust, e.g., insensitive to environmental and usage variation. Robustness (flex) studies are designed to challenge the system under conditions of stress to identify potential device deficiencies, including failures, and determine the robustness of the product.

The manufacturer must consider multiple skill levels of users, as well as potential instrument and reagent problems. Below is a list of factors that may need to be considered when performing robustness studies:

- 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, use of inappropriate anticoagulant, clotted specimens, error in specimen handling, incorrect specimen transport and/or storage, presence of interfering substances, 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, factors that may interfere with calibration
- Environmental factors including impact of key environmental factors (heat, 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.

The following should be provided:

- A summary of the evidence that falls within this category
- State 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

- If a performance study has been conducted that includes human factors/usability end points, reference to the studies and endpoints should be made, but full results do not need to be repeated

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

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 must have clinical evidence to support any clinical claims. This will include claims for clinical or diagnostic sensitivity and specificity.

7.4.1. Clinical evaluation – Manufacturer

All performance claims must be supported by well-designed performance evaluations that have been carried out or coordinated by the manufacturer.⁸

Provide the studies and the information identified in the introduction to Section 7, which must also include:

- Any anomalous results, or results that are not within predetermined specifications, should be clearly explained or justified
- 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
- 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 should be defined and spelled 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, providing the information identified in Section 7.4.1.
- If the study has been published in peer-reviewed scientific literature, provide publication details for the study.

⁸ 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 specimens obtained from populations equivalent to where this product will be supplied.

- 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 contain a complete set of labelling associated with the product. This includes:

- labels
- instructions for use (IFU)
- if applicable, the instrument manual
- any other instructional materials provided to the user

8.1. Labels

- Include copies of all packaging labels for the assay. This includes:
 - outer labels
 - component labels
- These labels must minimally include 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
 - 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, where possible
- Where a component is too small to contain all the above information, it must at a minimum contain Name, lot number expiration date, volume, and storage conditions.
- If the product requires associated instrumentation, the above requirements also apply to the instrument.
- The instrument should clearly display information regarding its status as a new or reprocessed product.

8.2. Instructions for use

The instructions for use will be reviewed for clarity, correctness, consistency with the information submitted in the dossier, and suitability for the target user group. The following must be submitted in the dossier:

- A copy of the current instructions for use
- The instructions for use should at a minimum include the following information⁹:
 - The product name and product code
 - The name and contact details of the manufacturer or an authorized representative of the manufacturer, in order for the user to obtain assistance
 - 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 (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

⁹ Labeling requirements that apply to the WHO prequalification of diagnostics programme are based on the document GHTF/SG1/N70:2011 Labeling for Medical Devices.

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 should 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 stat
- 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
- 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.¹⁰
- Precautions and measures to be taken in the event of performance changes or product malfunction
- Limitations of the assay, including information on interfering substances that may affect the performance of the assay
- 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
- Any requirements for special training or particular qualifications of the assay user

¹⁰ For more information see ISO 14971:2007 Medical devices - Application of risk management to medical devices.

- 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

8.3. Instrument manual

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

8.4. Any other instructional materials provided to the user

- 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 of **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**. This includes:
 - how the users are trained in the operation of the assay
 - how the users of the product contact the supplier/manufacturer for technical support
 - if there are representatives located in each country of supply to provide technical support
 - 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 provides the following information:

- A list of all adverse events 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 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

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 in vitro IVD under assessment, if applicable, include:
 - A list of National Regulatory Authorities that 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
- 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. **The certificates must be certified copies.** The manufacturer need not involve a notary public, and can instead certify the copies themselves. The manufacturer may be asked to present the original copy at any time.
- Details regarding any situations in which this 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.
- 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, system documents and procedures

These controlled documents and procedures are developed by the company to guide all operational aspects associated with the products for prequalification.

- Include a copy of the current version of the manufacturer's quality manual.¹⁴ The following aspects should be addressed (or referred to) in the quality manual¹⁵:
 - 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
- Provide an organizational chart for the manufacturer (if not already available within the quality manual)
- Provide a complete list of all valid quality management system documents, with the document title and document number, relevant to this product should be included
- Provide the documented procedure/s 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

- Provide the documented procedure/s, relevant to risk management planning and implementation
- Provide the documented procedure/s, relevant to control of non-conforming goods, including but not limited to procedures for corrective and preventative actions, recalls, field safety notices etc.
- Provide the documented procedure/s, relevant to the control of the key suppliers noted in Section 6.1.1. Design overview.

11.2. 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 the certified copies of certificates provided clearly demonstrate that the manufacture of the product under assessment is within the scope of the certification.
 - **The two previous inspection reports** issued by the certification body, related to the ISO 13485:2003 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 14969:2004 *Medical devices—Quality management systems-Guidance on the application of IS 13485:2003*
- ISO/TR 10013:2001 *Guidelines for quality management system documentation* [International Organization for Standardization (ISO) document; www.iso.org]
- ISO 18113:2009 *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 *Clinical laboratory testing and in vitro diagnostic test systems – 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 In vitro diagnostic medical devices – Measurement of quantities in biologic samples – Meteorological traceability of values assigned to calibrators and control materials
- ISO 15194:2009 In vitro diagnostic medical devices -- Measurement of quantities in samples of biological origin -- Requirements for certified reference materials and the content of supporting documentation
- ISO 14971:2007 Medical devices - Application of risk management to medical devices
- ISO 236:2011 In vitro diagnostic medical devices – Evaluation of stability of in vitro diagnostic reagents
- 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/N68:2012 Essential Principles of Safety and Performance of Medical Devices
- GHTF/SG1/N70:2011 Label and Instruction Use for Medical Devices
- GHTF/SG2/N54R8:2006 Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices
- GHTF/SG2/N57R8:2006 Medical Devices Post Market Surveillance: Content of Field Safety Notices
- 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 IVD. The EP checklist also allows easy identification of relevant documents and data for conformity assessment purposes.

The contents of the checklist vary among IVDs. More complex IVDs 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.

Note: An example of a completed EP checklist can be found in the "WHO Sample Product Dossier for WHO Prequalification" PQDx_170.
(refer to http://who.int/diagnostics_laboratory/evaluations/PQDxInfo/en/)

14.1. How to fill in the checklist

14.1.1. Identity of the IVD

The manufacturer should identify the IVD, 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 IVD? 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.

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.

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 product dossier.

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/N68:2012.

Essential Principles Checklist

Identity of the IVD:

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 Medical devices should achieve the performance intended by the manufacturer and be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose.				
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 All known and foreseeable risks, and any undesirable effects, should be minimised and be acceptable when weighed against the benefits of the intended performance of medical devices during normal conditions of use.				
Design and Manufacturing Requirements				
5.7 Chemical, physical and biological properties				
<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. 				

Essential Principle	Applicable to the device?	Method Used to Demonstrate Conformity	Method Reference	Reference to Supporting Controlled Documents
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.				
5.7.3 ----- etc. -----				
5.7.4 ----- etc. -----				
5.7.5				
5.7.6				