



Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

FINAL DOCUMENT

Title: Submission Dossier for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices

Authoring Group: Work Group 2, Pre-market: IVDD

Date: 26 November 2016

Dr. Wen-Wei Tsai

Chair, Work Group 2

Table of Contents

1.0	Introduction	4
2.0	Rationale, Purpose and Scope	5
2.1	Rationale	5
2.2	Purpose.....	5
2.3	Scope.....	5
3.0	References	6
4.0	Definitions	7
5.0	General Principles	7
6.0	Elements of the Submission Dossier	10
6.1	Executive Summary	10
6.2	Relevant Essential Principles and Method Used to Demonstrate Conformity	11
6.3	Device Design.....	13
6.4	Device description and features	13
6.5	Intended use	14
6.6	Limitations	15
6.7	Warnings and precautions.....	15
6.8	Components	16
6.9	Reagent stability.....	16
6.10	Product Verification and Validation Documents.....	18
6.10.1	Analytical Performance Characteristics.....	18
6.10.2	Clinical Performance Characteristics.....	22
6.10.3	Software: Verification and Validation	26
7.0	Labelling for IVD Medical Device	26
8.0	Risk Analysis.....	27
9.0	Manufacturing Process	28
10.0	Declaration of Conformity	29
Annex A.	30

Preface

This document was produced by the Asian Harmonization Working Party, based on the Global Harmonization Task Force Document, “Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices”, GHTF/SG1/N063:2011 of GHTF Study Group 1 and the ASEAN Common Submission Dossier Template (CSDT) which is based on the GHTF document GHTF/SG1/N011:2008 “Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)”.

The AHWP also acknowledges and has considered, the document “In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC)” developed by the International Medical Device Regulators Forum (IMDRF), which provides an internationally harmonized, modular, format for use when filing In Vitro Diagnostic (IVD) medical device submissions to regulatory authorities for market authorization.

This document is intended to provide non-binding guidance for use in the regulation of IVD medical devices, and has been subject to consultation throughout its development.

There are no restrictions on the reproduction, distribution, translation or use of this document. However, incorporation of this document, in part or in whole, into any other document does not convey or represent an endorsement of any kind by the Asian Harmonization Working Party.

1.0 Introduction

The objective of the Asian Harmonization Working Party (AHWP) is to encourage convergence at the worldwide level in the evolution of regulatory systems for medical devices, including IVD medical devices, in order to protect the public health by those regulatory means considered the most suitable.

The primary way in which the Asian Harmonization Working Party (AHWP) achieves its goals is through the production of harmonized guidance documents suitable for implementation or adoption by member Regulatory Authorities, as appropriate taking into account their existing legal framework, or by member economies with developing regulatory programmes. Eliminating differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

This guidance document is one of a series that together describe a regulatory model for medical devices, including IVD medical devices. It provides recommendations on the content of the dossier to be assembled, and where required, submitted to a Regulatory Authority or Conformity Assessment Body, and its role in demonstrating conformity to the *Essential Principles of Safety and Performance of IVD Medical Devices*.

This document is intended for use by Regulatory Authorities (RA), Conformity Assessment Bodies (CAB) and industry, and will provide benefits in establishing, in a consistent way, an economic and effective approach to the control of IVD medical devices in the interest of public health.

Regulatory Authorities that are developing regulations or amending existing ones are encouraged to consider the adoption of this guidance and the principles it embodies, as this will help to reduce the diversity of schemes worldwide and facilitate the process of harmonization.

Work Group 2 of the AHWP has prepared this guidance document. Comments or questions should be directed to the Chair of AHWP Work Group 2 whose contact details may be found on the AHWP web page (<http://www.ahwp.info/>).

2.0 Rationale, Purpose and Scope

2.1 Rationale

This document aims to provide guidance on the common template for the preparation of a submission dossier for the purpose of a product registration application for IVD medical devices. In particular, this document serves to describe the technical information to be submitted in each section.

The ASEAN CSDT for IVD medical devices contains detail which may enhance the GHTF STED for IVD medical devices; the combination of the two documents form the basis of these AHWP recommendations for a common submission file for IVD medical devices.

The IMDRF document defines the location of both common (IMDRF) and regional (IMDRF members only) content for all submission types. The ToC documents are intended to work together with a separate document created for each participating jurisdiction, and so not all headings in the ToC are required for all submission types and/or IMDRF jurisdictions. The ToC is not restricted to requirements for technical documentation, although the requirements for technical documentation cover the same headings as in this AHWP document. The detail provided herein may therefore be useful in reviewing a submission prepared for an IMDRF member jurisdiction, but the recommendations for submission format may differ.

2.2 Purpose

The document is intended to provide guidance for submission of IVD medical device information to the regulatory authorities. It is envisaged that a common template for submission dossiers will harmonize the differences in documentation formats that presently exist in different AHWP member economy jurisdictions. The adoption of this guidance document in AHWP member economies will eliminate the preparation of multiple dossiers, arranged in different formats but with essentially the same contents, for regulatory submission to different regulatory authorities.

2.3 Scope

This guidance document describes the format for an AHWP member economy harmonized submission dossier and provides general recommendation on the content of the formatted elements. This document does not recommend any new or additional technical documents above and beyond what should be created by the manufacturer to comply with existing requirements to demonstrate conformity to the AHWP guidance document on *Essential Principles of Safety and Performance of IVD Medical Devices*.

This document applies to all products that fall within the definition of IVD medical device as provided in the AHWP guidance document on *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*.

Essentially, the submission dossier contains elements of the technical documentation collated for the purpose of demonstrating conformity to the Essential Principles of Safety and Performance of IVD medical devices.

The format of the submission dossier recommended herein is based upon the goal of both regulators and manufacturers to strive for the least burdensome means to demonstrate conformity to the Essential Principles for all classes of IVD medical devices.

3.0 References

AHWP/WG1a/F002:2013 (now restructured to WG2) *Essential Principles of Safety and Performance of IVD Medical Devices*

AHWP/WG2-WG8/F002:2014 *Role of Standards in the Assessment of Medical Devices*

AHWP/WG5/F003:2015 *Clinical Evidence for IVD Medical Devices - Key Definitions and Concepts*

AHWP/WG5/F004:2015 *Clinical Evidence for IVD Medical Devices- Scientific Validity Determination and Performance Evaluation*

AHWP/WG2_WG1/F001:2015 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*

AHWP/WG2/WD001:2016 *Principles of In Vitro Diagnostic Medical Devices Classification*

AHWP/WG2/WD002:2016 *Principles of Conformity Assessment for In Vitro Diagnostic Medical Devices*

ASEAN Medical Device Directive, version 11, 08 May 2012

GHTF/SG1/N70:2011 *Label and Instructions for Use for Medical Devices*

GHTF/SG1/N11:2008 *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)*

GHTF/SG5/N8:2012 *Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices*

ISO 18113-1:2009 *In vitro diagnostic medical devices -- Information supplied by the manufacturer (labelling) -- Part 1: Terms, definitions and general requirements*

4.0 Definitions

Calibrator: Measurement standard used in the calibration of an IVD instrument or system.

Control material: Any substance, material or article intended by its manufacturer to be used to verify the performance characteristics of an IVD medical device.

Instrument: Any equipment or apparatus intended by the manufacturer to be used as IVD Medical Device.

In Vitro Diagnostic (IVD) Medical Device: The term is as defined in *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*.

Lay Person: Individual without formal training in a relevant medical field or discipline.

Near Patient Testing: Testing performed outside a laboratory environment by a healthcare professional not necessarily a laboratory professional, generally near to, or at the side of, the patient. (Also known as Point-of-Care Testing (POC)).

Performance Evaluation for an IVD medical device: assessment and analysis of data to establish or verify the performance of an IVD medical device, where:

- Analytical performance: the ability of an IVD medical device to detect or measure a particular analyte.
- Clinical performance: the ability of an IVD medical device to yield results that are correlated with a particular clinical condition/physiological state in accordance with target population and intended user.

Reagent: Chemical, biological or immunological preparations intended by the manufacturer to be used as IVD medical devices.

Recognised Standard: Standard deemed to offer the presumption of conformity to specific essential principles of safety and performance.

Self-testing: Testing performed by lay persons.

Submission Dossier: a formatted compilation of documents and elements of the technical documentation to be submitted for conformity assessment purposes.

5.0 General Principles

Manufacturers of all Classes of IVD medical devices are expected to demonstrate conformity of the IVD medical device to the *Essential Principles of Safety and Performance of IVD Medical Devices*¹, through the preparation and holding of a submission dossier that

¹ AHWP/WG1a/F002:2013 *Essential Principles of Safety and Performance of IVD Medical Devices*

shows how each IVD medical device was developed, designed and manufactured together with the descriptions and explanations necessary to understand the manufacturer's determination with respect to such conformity.

For the purpose of conformity assessment by a RA/CAB, the manufacturer assembles the submission dossier, including a synopsis from existing technical documentation to provide evidence to the RA/CAB that the subject IVD medical device is in conformity with the Essential Principles. The submission dossier reflects the status of the IVD medical device at a particular moment in time (e.g. at the moment of premarket submission or when requested by a RA for post-market purposes) and is prepared in order to meet regulatory requirements.

Where the submission dossier is submitted to a RA/CAB, it should be in a language acceptable to the reviewing organisation.

The prepared submission dossier shall contain all sections, i.e. sections 6.0.to10.0. Where there are sections not applicable to the IVD medical device, the reason for the non-applicability should be provided under the section heading.

The depth and detail of the information contained in the submission dossier will primarily depend on the classification of the subject IVD medical device.

In addition to classification, further considerations when developing the individual sections of the submission dossier include for example:

- a high degree of complexity in the subject IVD medical device.
- the IVD medical device incorporates novel technology;
Examples of novel technology include:
 - there has been no such IVD medical device available on any market for the relevant analyte (measurand);
 - the procedure involves analytical technology not used in connection with a given analyte (measurand) or other parameter on the market.
- the IVD medical device is an already marketed IVD medical device type that is being offered for a different intended use;
- the IVD medical device type has been associated with a significant number of adverse events known to the manufacturer, including use errors, AHWP/WG2/F001:2013 *Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative* (the post-market work group, previously WG2, is now restructured to WG4);
- the IVD medical device incorporates novel or hazardous materials of concern;
- the IVD medical device raises specific public health concerns (e.g. virulent influenza pandemic).

The submission dossier should contain:

- summary information on selected topics, and may contain detailed information on specific topics. 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 and assess the validity of that information.

- an Essential Principles checklist (EP checklist).
The EP checklist is created as part of the manufacturer's submission dossier and is controlled by the manufacturer's QMS. It provides a tabular overview of the Essential Principles and identifies those that are applicable to the IVD medical device, the chosen method of demonstrating that the device conforms to each relevant Essential Principle and the reference to 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 submission dossier submitted to RA/CAB. The cited references to the controlled documents also allow easy identification of additional relevant documents and data.

Note:

- a) all copies of labelling, certificates, reports and other documents submitted must be legible ;
- b) copies of labelling, certificates and reports that are referenced within the submission dossier may be submitted as annexes;
- c) where supporting documents such as reports or certificates are provided, every document must be submitted in full, i.e. all the pages of a document must be submitted;
- d) all certificates submitted must be within their validity period.

Guidance:

For the purpose of the submission dossier, 'summary' and 'detailed information' are defined as:

Summary Information

A summary should provide enough information to allow the RA/CAB to assess the validity of that information. This summary should contain a brief description of:

- a) the study protocol,
- b) the study results,
- c) the study conclusion.

This summary may include:

- a) Where a recognized standard exists, a declaration/certificate of conformity to a recognized standard can be provided with a summary of the data if no acceptance criteria are specified in the standard;
- b) In the absence of a recognized standard, a declaration/certificate of conformity to a published standard that has not been recognized might be provided if it is supported by a rationale for its use, and summary of the data, and a conclusion, if no acceptance criteria are specified in the standard;
- c) In the absence of a recognized standard and non-recognized published standards, a professional guideline, industry method, or in-house standard may be referred to in the summarized information. However, it should be supported by a rationale for its use, a description of the method used, a

summary of the data in sufficient detail and a conclusion to allow assessment of its adequacy;

- d) A review of relevant published literature regarding the device/analyte (measurand) or substantially similar IVD medical devices.

Detailed Information

Detailed information should include:

- a) the complete study protocol,
- b) the method of data analysis,
- c) the complete study report,
- d) the study conclusion.

For detailed information, when a recognized standard exists that contains the protocol and the method of data analysis, this information can be substituted by a declaration/certificate of conformity to the recognized standard. However, a summary of the data and conclusions should be provided.

For clinical performance (which is part of the clinical evidence), the detailed information will typically include individual data points (formatted raw data) for a Class D IVD medical device.

Where appropriate, actual test result summaries with their acceptance criteria should be provided and not just pass/fail statements.

6.0 Elements of the Submission Dossier

6.1 Executive Summary

An executive summary shall include the following information:

- an overview, e.g., introductory descriptive information on the IVD medical device,
 - the intended use,
 - any novel features where applicable.
- commercial marketing history;
- regulatory approval or marketing clearance obtained in the country of manufacturer, if applicable, and major market such as IMDRF or AHWP member economies;
- status of any pending request for market clearance; and
- important safety and/or performance related information.

Guidance:

- a) If the IVD medical device contains any **novel features**, e.g. Next Generation Sequencing (NGS), a description of the novel feature is to be provided.

- b) For **commercial marketing history**, the list of countries where the IVD medical device is marketed, the year of the first introduction on the global market and the number of IVD medical devices sold in total.
- c) The registration status (i.e. submitted, not submitted, pending approval, rejected or withdrawn) and intended use and indications of the IVD medical device in the country of manufacturer, if applicable, and major markets such as IMDRF or AHWP member economies. This information is to be provided in a tabular format as given below:

Country/ jurisdiction	Regulatory authority (RA)	Intended use	Registration status and date	Reason for rejection or withdrawal (<i>if applicable</i>)

- d) For **important safety and/or performance related information**, a summary of reportable adverse events and field safety corrective actions (FSCA) for the IVD medical device since its first introduction on the global market is to be provided.

For reported adverse events:

- Number of adverse events which occurred in the last 3 years.
- Frequency of occurrence (number of reports / total units sold).
- Countries where the adverse events happened.

For reported field safety corrective actions (FSCAs):

- Number of FSCA which occurred in the last 3 years.
- Frequency of occurrence (number of reports / total units sold).

Three years is considered to be appropriate time given the lifecycle of IVD medical device. If there are no any adverse events or FSCAs for the past 3 years, an attestation is required.

6.2 Relevant Essential Principles and Method Used to Demonstrate Conformity

The submission dossier should identify the Essential Principles of Safety and Performance of IVD Medical Devices that are applicable to the device. Not all the essential principles will apply to all devices and it is for the manufacturer of the device to assess which are appropriate for his particular device product. In determining this, account must be taken of the intended use of the device.

The submission dossier should identify the general method used to demonstrate conformity to each applicable Essential Principle.

The methods that may be used to demonstrate conformity may include one or more of the following:

- a) conformity with recognized or other standards;

- b) conformity with a commonly accepted industry test method;
- c) conformity with appropriate in-house test methods that have been validated and verified;
- d) comparison to an IVD medical device already available on the market.

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

The evidence of conformity can be provided in tabular form with supporting documentation available for review as required. A sample of the Essential Principles conformity checklist is included in Appendix A.

For example, a completed Essential Principles conformity checklist can be used to demonstrate that a recognized standard was used as part of the method to demonstrate conformity to one Essential Principle. As such, the submission dossier would then include a declaration of conformity to the standard or other certification permitted by the Regulatory Authority, and a summary of the test data, if the standard does not include performance requirements. When the manufacturer uses international or other standards to demonstrate conformity with the Essential Principles, the submission dossier should identify the full title of the standard, identifying numbers, date of the standard, and the organization that created the standard. When the manufacturer uses other means, such as internal standards, the submission dossier should describe the means.

Guidance:

The Essential Principles (EP) conformity checklist is to be prepared based on EP document of AHWP, AHWP/WG1a/F002:2013 (now restructured to WG2). The IVD medical device to which the EP conformity checklist is applicable should be identified on the checklist itself. Where applicable, the various configurations of the IVD medical device covered by the checklist are to be identified in the checklist. The columns in the recommended format for the checklist should be completed as follows:

- a) Applicable to the IVD medical device?

Either a 'Yes' or 'No' answer is required. If the answer is 'No' this should be briefly explained. For example: For an IVD medical device that is a reagent, the answer to EP C8 would be 'No – The IVD medical device is not an instrument, and therefore, EMC requirements do not apply.'

- b) Method of conformity

State the title and reference of the standard(s), industry or in-house test method(s), comparison study(ies) or other method used to demonstrate compliance. For standards, this should include the date of the standard and where appropriate, the clause(s) that demonstrates conformity with the relevant

EP. Where a standard is referred to more than once in the checklist, the reference number and date can be repeated.

c) Identity of specific documents

This column should contain the reference to the actual document(s) in the technical documentation that demonstrate(s) compliance to the EP, i.e. the certificates, test reports, study reports or other documents that resulted from the method used to demonstrate compliance, and its location within the submission dossier.

6.3 Device Design

The submission dossier should contain information to allow a reviewer to obtain a general understanding of the design applied to the IVD medical device.

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 IVD medical device.

For instruments this would include a description of major subsystems, analytical technology (e.g. operating principles, control mechanisms), dedicated computer hardware and software.

For instruments and software, an overview of the entire system would be required, including an Architecture Design Chart which is typically a flowchart of the relationships among the major functional units in the software, including relationships to hardware and to data flows such as networking.

For standalone software, this would typically include a description of the data interpretation methodology (i.e. algorithms).

For self-testing devices the design should include a description of the design aspects that make it suitable for lay person use.

Typically for a Class D IVD medical device detailed information on material specifications would be provided.

This section is not intended to take the place of the more detailed information required for a QMS audit or other conformity assessment activity. If design takes place at multiple sites, a controlling site must be identified.

6.4 Device description and features

The submission dossier should include the following device descriptive information:

- a) the Class of the device and the applicable classification rule according to *Principles of In Vitro Diagnostic Medical Devices Classification*;
- b) the short description of the intended use of the IVD medical device;
- c) the intended user (lay person or professional);
- d) a general description of the principle of the assay method or instrument principles of operation sufficient to allow the reviewer to understand the key elements of the principle e.g. Antibody-antigen-antibody sandwich assay, FISH assay, chemiluminescence, flowcytometry;
- e) a description of the components (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).

and where applicable:

- f) a description of the specimen collection and transport materials provided with the IVD medical device or descriptions of specifications recommended for use;
- g) for instruments of automated assays: a description of the appropriate assay characteristics or dedicated assays;
- h) for automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation;
- i) a description of any software to be used with the IVD medical device;
- j) a description or complete list of the various configurations/variants of the IVD medical device that will be made available;
- k) a description of the accessories, other IVD medical devices and other products that are not IVD medical devices, which are intended to be used in combination with the IVD medical device.

Guidance:

- a) A description of various configurations of the IVD medical device may include a list of the devices to be registered as a family or group, if applicable. For example, a family of pregnancy rapid tests can consist of devices available in different configurations, such as a test strip or in a cassette.
- b) A description of the accessories, other IVD medical devices and other products that are not IVD medical devices, which are intended to be used in combination with the IVD medical device may include, for example, a lancet, which is a medical device and not an IVD medical device that is provided in the package to the user to perform a test.
- c) The use of diagrams, photographs or drawings, as appropriate, is considered helpful and is encouraged

6.5 Intended use

This means the use for which the medical device is intended, and for which it is suited according to the data supplied by the manufacturer in the instructions for use as well as the functional capability of the device.

Guidance:

The intended use of an IVD medical device should include information on the following:

- a) What is detected, type of analyte or measurand of the assay.
- b) Whether the test is quantitative or qualitative.
- c) Role of the testing in the clinical context e.g. screening, diagnostic or detection, aid to diagnostic, monitoring.
- d) the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate.
- e) Type of specimen to be used e.g. serum, plasma, whole blood, tissue biopsy, urine etc.
- f) The intended users (e.g. self-testing by lay person, near-patient by trained personnel or professionals).
- g) Assay type e.g. immunoassay, chemistry, cytochemistry, image analysis, immunohistochemistry.
- h) The specific name of the instrument required for the assay, if any.
- i) Testing population, e.g. blood donors, paediatric patients, etc.

6.6 Limitations

This is a general description of the disease or condition and the patient population for which the device should not be used for the purpose of diagnosing, treating, curing or mitigating. It should also include the limitations of the analytical method or procedure.

Guidance:

Specimens from patients who have received preparations of mouse monoclonal antibodies for therapy may not be used with assay kits which employed mouse monoclonal antibodies. It may show either falsely elevated or depressed values.

6.7 Warnings and precautions

This alerts the user to exercise special care necessary for the safe and effective use of the device. They may include actions to be taken to avoid effects on patients/users that may not be potentially life-threatening or result in serious injury, but about which the user should be aware. Precautions may also alert the user to adverse effects on the device of use or misuse and the care necessary to avoid such effects.

Guidance:

For products containing biological material such as potential infectious agents, radioactive material, and any other hazardous material, safety warnings must be included. The related safety and environmental regulations should be followed.

6.8 Components

This section must include complete details of the components, which may include raw materials, and their specifications.

- a) All active ingredients should be chemically or biologically characterised. Documentations should be included such as a certificate of analysis from the vendor.
- b) For components of biological or recombinant origin, the source must be indicated and details on production must be provided. These details would include the strain of the virus, the cell line for cultivation of the virus, animal source, sequences of relevant nucleic acids and amino acids, purified proteins, recombinant and synthetic proteins as appropriate.
- c) If applicable, process validation results to be provided to substantiate that manufacturing procedures are in place to minimise biological risks, in particular, with regard to viruses and other transmissible agents. This also includes inactivation of infectious organisms in reagents and the production of reagents.
- d) if applicable, information to be provided on irradiating components, non-ionising or ionising (e.g. Iodide-131 in the Radioimmunoassay kit, radio-labelled Phosphorus-32 DNA probes in Southern blots)

Guidance:

The information in this section helps regulators in assessing the rigor of the risk analysis and factors such as purity, safety and performance.

6.9 Reagent stability

Data on stability of reagent should include information on the recommended shelf life or storage conditions for in use or opened and unopened IVD medical devices, and also taking into consideration variable conditions including temperature, freeze/thaw cycle and duration during usage (including for on-board use), and for transportation. The studies should be provided from at least 3 lots/batches. If real-time stability is not available, an accelerated study is acceptable for initial shelf life claim while continuing real time studies to be performed with justification. Information on the statistical method used also should be provided. The final real time study report may be requested by some regulators.

Guidance:

More details can be found in the document *In vitro diagnostic medical devices - Evaluation of stability of in vitro diagnostic reagents* (ISO 23640:2011/ EN ISO 23640:2013)

- a) Claimed shelf life

The information on stability testing should include data 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).

Typically for Class C and D IVD medical devices, detailed information would be provided.

Such detailed information should describe:

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

a) In use stability

Information should also be provided 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 describe:

- i) the study report (including the protocol, acceptance criteria and testing intervals);
- ii) conclusions and claimed in use stability.

Typically for Class C and D IVD medical devices, detailed information would be provided.

c) Shipping stability

Information should be provided 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 heat and/or cold.

Such information should describe:

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

Typically for a Class C and D IVD medical device, detailed information would be provided.

6.10 Product Verification and Validation Documents

The information provided in the product verification and validation section of the submission dossier will vary in the level of detail as determined by the classification of the device.

Also other characteristics as outlined in section 5.1 will influence the level of detail of the submission dossier.

As a general rule, the submission dossier should summarise the results of verification and validation studies undertaken to demonstrate conformity of the IVD medical device with the Essential Principles that apply to it. Where appropriate, such information might come from the literature.

Guidance:

For all aspects of verification and validation described in this section, where no testing was undertaken for the IVD medical device, a rationale for that decision must be provided. Evidence to support the rationale shall be provided.

6.10.1 Analytical Performance Characteristics

The statements and descriptions in the following sections refer to all IVD medical devices. It must be noted however that there are applicability differences between instrumentation and reagent-based assays, and that the assays themselves may be quantitative, semi-quantitative or qualitative in nature. There may be limited applicability of some of the following subsections for qualitative or semi-quantitative assays. Where possible, comments regarding instrumentation or qualitative assays appear in the subsections.

6.10.1.1 Specimen type

This section should describe the different specimen types that can be used. This should include their stability and storage conditions and is typically applicable to all systems and assay types.

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

This section should include summary 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 type tested, number of samples, sample range (using spiked samples as appropriate) or target concentrations tested, calculations and statistical methods, results and conclusions.

Typically for a Class D IVD medical device, detailed information would be provided.

6.10.1.2 Accuracy of measurement

This section should describe both trueness and precision studies.

Note: 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.

While measurement **trueness**, affected by systematic error, is normally expressed in terms of bias, 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.

6.10.1.2.1 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 means selected to establish the trueness. Trueness measures apply to both quantitative and qualitative assays only when a reference standard or method is available.

Typically for Class C and D IVD medical devices, detailed information would be provided.

6.10.1.2.2 Precision of measurement

This section should describe repeatability and reproducibility studies.

6.10.1.2.2.1 Repeatability

This section should include repeatability estimates and information about the studies used to estimate, as appropriate, within-run variability. Repeatability data is obtained for instrumentation in conjunction with an appropriate assay.

Typically for Class C and D IVD medical devices, detailed information would be provided.

Note 1: Such studies should include the use of samples that represent the full range of expected analyte (measurand) concentrations that can be measured by the test as claimed by the manufacturer.

Note 2: If a recognized standard is used, a declaration/certificate of conformity to the recognized standard along with a summary of the data and conclusions should be provided.

6.10.1.2.2.2 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**”. Reproducibility data is obtained for instrumentation in conjunction with an appropriate assay.

Typically for Class C and D IVD medical devices, detailed information would be provided.

Note 1: Such studies should include the use of samples that represent the full range of expected analyte (measurand) that can be measured by the test as claimed by the manufacturer.

Note 2: If a recognized standard is used, a declaration/certificate of conformity to the recognized standard along with a summary of the data and conclusions should be provided.

6.10.1.3 Analytical sensitivity

This section should include 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 should also be provided as well as a description of the calculation used to determine assay sensitivity. For example:

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

Typically for a Class C and D IVD medical devices, detailed information would be provided.

6.10.1.4 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.

Information should be provided 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, analyte (measurand) test concentration, and results.

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:

- a) substances used for patient treatment (e.g. therapeutic drugs, anticoagulants, etc.);
- b) substances ingested by the patient (e.g. over the counter medications, alcohol, vitamins, foods, etc.);
- c) substances added during sample preparation (e.g. preservatives, stabilizers);
- d) substances encountered in specific specimens types (e.g. haemoglobin, lipids, bilirubin, proteins);
- e) 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.

Typically for Class C and D IVD medical devices, detailed information would be provided.

6.10.1.5 Measuring range of the assay

This section should include a summary of 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 summary should include a description of specimen type, number of samples, number of replicates, and preparation including information on matrix, analyte (measurand) levels and how levels were established. If applicable, add a description of high dose hook effect and the data supporting the mitigation (e.g. dilution) steps.

Typically for Class C and D IVD medical devices, detailed information would be provided.

6.10.1.6 Definition of assay cut-off

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

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

Typically for Class C and D IVD medical devices, detailed information would be provided.

6.10.1.7 Metrological traceability of calibrator and control material values

Where applicable, summarize the information about 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. 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.

Typically for a Class D IVD medical device, detailed information would be provided.

6.10.2 Clinical Performance Characteristics

Where relevant, the submission dossier should contain data on the clinical performance of the IVD medical device.

This clinical performance data is one of the elements of clinical evidence that demonstrates the conformity of the IVD medical device to the Essential Principles that apply to it.

Note: Analytical performance and clinical performance are elements of clinical evidence. More detailed recommendations regarding these elements of the submission dossier are provided in guidance developed by GHTF and by AHWP WG5.

Guidance:

The clinical evidence to be provided should include the information mentioned in this section.

For a Class D IVD medical device, if discrepant test results are identified as part of an evaluation, these results shall be resolved as far as possible, using one or more of the following approaches:

- by evaluation of the discrepant sample in further test systems,
- by use of an alternative method or marker,
- by a review of the clinical status and diagnosis of the patient, and
- by the testing of follow-up-samples.

a) Clinical (Diagnostic) Sensitivity

Data on clinical (diagnostic) sensitivity should include information on the following:

- i) The methodology including its statistical method, results, discussion and conclusion for the study;
- ii) The total individual positive specimens and the sero-conversion panels used in the study. For positive specimens, where different virus subtypes and genotypes are available, studies of these subtypes specimens must be included. For Class D IVD medical device, when testing the sero-conversion specimens, the diagnostic sensitivity during the early infection phase (sero-conversion) has to represent the state of the art;
- iii) The probability that the IVD medical device gives a positive result in the presence of the target marker, which is calculated as the $\frac{\text{true positives}}{\text{true positive} + \text{false negative}}$; and
- iv) Positive Predictive Values (PPV) is calculated as the $\frac{\text{true positives}}{\text{true positives} + \text{false positives}}$.

b) Clinical (Diagnostic) Specificity

Data on clinical (diagnostic) specificity should include information on the following:

- i) The methodology including its statistical method, results, discussion and conclusion for the study;
- ii) The total individual negative specimens in the study. Negative specimens used in a performance evaluation shall be defined so as to reflect the target population for which the test is intended, for example blood donors, clinical

samples or hospitalised patients including pregnant women, and potentially interfering samples;

- iii) The probability that the IVD medical device gives a negative result in the absence of the target marker which is calculated as the *true negatives/(true negatives + false positives)*; and
- iv) Negative Predictive Values (NPV) is calculated as the *true negatives/(true negatives + false negatives)*.

c) Comparison Studies Using Clinical Specimens

Comparison studies using clinical specimens should include information on the following:

i) Method comparison

All performance evaluations shall be carried out in direct comparison with an established state of the art IVD medical device. The established product for comparison must have obtained marketing clearance from any of the reference agencies, such as TGA Australia, Health Canada, EU, MHLW Japan, and US FDA.

Study design should include:

- description on the test methods,
- information on the comparator(s) (e.g., reference IVD medical device, reference method),
- the sample type(s) (e.g., unaltered patient specimens, spiked or diluted patient specimens, spiked patient pools, and control material), matrix, number of samples, sample range,
- when appropriate, number/types of sites, sample selection methods, inclusion/exclusion criteria, overall demographic description of patients represented by the samples (e.g., age, gender, race, how/whether samples represent the intended use population), number of individuals represented, and
- statistical methods used to generate results (e.g., regression methods, data exclusion, number of observation represented by each data point).

Results should include:

- Description on the overall results and/or results from specific sites and patient groups, as appropriate,
- For quantitative tests, information such as slope and intercept (with confidence intervals), correlation coefficient, measure of scatter around the regression line, measure of bias at medical decision levels. In some cases, a graph (x-y graph or bias plot) can be included, and
- For qualitative or semi-quantitative tests, percent agreement with comparator for positive/negative samples, confidence intervals.

ii) Matrix comparison:

Study design should include:

- for each matrix in the intended use, the method for comparison or determination of accuracy, and
- sample types tested, number of samples, sample range or target concentrations tested and calculations/statistical methods.

Results/Acceptance criteria should include:

- the accuracy of the new matrix or results of the matrix comparison.

d) Clinical Cut-off

This information should include:

- i) The established cut-off and its validation for the new IVD medical device; and
- ii) If applicable, the “equivocal zone” is to be defined, and include a description of how results within this zone are reportable to the user.

e) Reference Interval (Expected Values)

This information should include:

- i) The reference interval for this measured and the method used to determine it;
- ii) The literature references establishing the reference intervals and justification for applying this range to the new IVD medical device;
- iii) A description of the methods for determining the reference intervals if they are not well established from the literature or if the range cannot be transferred to the new IVD medical device;
- iv) The description of the population studies (demographics, inclusion/exclusion criteria, number of individuals);
- v) Any separate reference intervals for subclasses where clinically justified;
- vi) The method of clinical diagnosis of the reference population(s); and
- vii) The statistical method used to calculate the ranges.

f) Additional requirements for IVD medical device for self-testing and near patient testing (if applicable)

The field evaluation report should be provided. Study results and data should:

- i) show the handling suitability of the IVD medical device; and
- ii) determine the IVD medical device’s performance when used by the intended users following instructions provided in the labelling and without the assistance from the professionals.

6.10.2.1 Use of Existing Bibliography

Copies should be provided of all literature studies, or existing bibliography, that the manufacturer is using to support safety and performance. These will be a subset of the bibliography of references. General bibliographic references should be IVD-specific and supplied in chronological order. Care should be taken to ensure that the references are timely and relevant to the current application.

Evidence of clinical performance may comprise device-related performance studies conducted domestically or other countries. It may be derived from relevant publications in a peer-reviewed scientific literature. The documented evidence submitted should include the objectives, methodology and results presented in context, clearly and meaningfully.

The conclusions on the outcome of the clinical evaluation should be preceded by a discussion in context with the published literature

Guidance:

Critical review analysis and evaluation of literature studies or existing bibliography are broad concepts, which include any experience gained from an established IVD medical device already on the market and used in clinical practice. A written report containing a critical review analysis and evaluation of the literature studies compilation must include the objectives, methodology, results, discussion and a conclusion to demonstrate that such data support the intended purpose, the design, the materials, its procedures, the safety and performance of the IVD medical device.

6.10.3 Software: Verification and Validation

The correctness of a software product is a critical product characteristic that cannot be fully verified in a finished product. The manufacturer must provide evidence that validates the software design and development process. This information should include the results of all verification, validation and testing performed in-house and in a user's environment prior to final release, for all of the different hardware configurations identified in the labelling, as well as representative data generated from both testing environments.

7.0 Labelling for the IVD Medical Device²

The device labelling refers to any written, printed or graphic representation affixed to a medical device or any part of its packaging, or accompanying an IVD medical device, when the IVD medical device is being supplied.

The labelling includes:

² GHTF/SG1/N70:2011 *Label and Instructions for Use for Medical Devices*

- a) Labels on the device and its packaging;
- b) Instructions for use.

Any information and instructions given to the patient, including instructions for any procedure the patient is expected to perform (if applicable) should be provided.

7.1 Samples of Labels on the IVD Medical Device and its Packaging

This is the printed, written or graphic product information provided on or attached to one or more levels of packaging, including the outer packaging or the outside container wrapper. Any pack labelling, which is not provided on the outer packaging must be easily legible through this outer packaging.

If it is physically impossible to include samples of labels (e.g. large warning labels affixed onto instruments), alternative submission methods (e.g. photographs or technical drawings), to the extent appropriate, will suffice to meet the requirements of this section.

For inclusion in a submission dossier, the labelling should contain the final content as determined by the manufacturer but does not have to be in the final (printed) format.

7.2 Instructions for Use

These include all the necessary information from the manufacturer including the procedures, methods, and preparation to be followed for the use of the IVD medical device.

Guidance:

The submission dossier should typically contain a complete set of labelling associated with the IVD medical device as described in the GHTF document *Label and Instructions for Use for Medical Devices*.

8.0 Risk Analysis

The submission document 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. Preferably, this risk analysis should be based on recognised standards and be part of the manufacturer's risk management plan.

The summary should address possible hazards for the IVD medical device such as the risk from false positive or false negative results, indirect risks which may result from IVD medical device-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.

Typically for a Class D IVD medical device a detailed report would be provided.

Guidance:

Information required in this section should be provided in the form of a risk management report. It is recommended that the risk management activities be conducted according to ISO 14971. A risk management report will contain details of the risk analysis, risk evaluation, risk control conducted for the IVD medical device. The risks and benefits associated with the use of the IVD medical device should be described.

9.0 Manufacturing Process

The submission dossier should contain information to allow a reviewer to obtain a general understanding of the manufacturing processes. It is not intended to take the place of the more detailed information required for a QMS audit or other conformity assessment activity. This information may take the form of a process flow chart showing, for example, an overview of production including the technologies used, assembly and packaging of the finished IVD medical device. This section should include details of any in-process and final product testing (e.g. the manufacturer's QC release program).

This section should identify the sites where the activities above are performed (this does not include the sites of all suppliers of raw materials but only the sites that are involved in critical manufacturing activities). If QMS certificates, or the equivalent, exist for these sites, they may be annexed to the submission dossier.

Guidance:

- a) Information on the manufacturing process should be provided in sufficient detail to allow a general understanding of the manufacturing processes. Detailed proprietary information on the manufacturing process is not required. The information may be presented in the form of a process flow chart showing an overview of production, controls, assembly, in-process and final product testing, and packaging of the finished IVD medical device.
- b) If the manufacturing process is carried out at multiple sites, the manufacturing activities carried out at each site should be clearly identified. For example:
 - i) If the manufacturing process of a product consists of a number of sub-assembly processes, the manufacturing sites where each of these sub-assembly processes are carried out must be identified, and the relationship between these processes must be shown; or
 - ii) If multiple sites manufacture the same product, each of these sites must be identified. The sites (including contract manufacturers) where design and manufacturing activities are performed shall be identified.

- c) Quality Management System certificates may be provided for the design and manufacturing sites (including contract manufacturers) as an annex to the submission dossier. This requirement does not apply to raw material manufacturers (for example, contract manufacturers of sodium azide).
- d) For Class D IVD medical device, the batch release plan should be provided to demonstrate that each batch consistently identifies the relevant antigens, epitopes, and antibodies. The batch release plan may be provided as an annex, with detailed information on the establishment of the batch release panel, including the number of positive and negative specimens.

10.0 Declaration of Conformity

The Declaration of Conformity is not part of the submission dossier. However, it may be annexed to the submission dossier once the conformity assessment process has been completed. The content of the Declaration of Conformity is described in AHWP/WG2/WD002:2016 *Principles of Conformity Assessment for In Vitro Diagnostic Medical Devices*.

Annex A.

How to fill in the Essential Principles (EP) Checklist

a) Identity of the IVD medical device

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

b) Applicable to device?

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

c) 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.

d) Method reference

After having stated the method in the previous column, here the manufacturer should name the title and should 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.

e) Reference to supporting controlled documents

This column should contain the reference to the actual submission dossier 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, if included in the submission dossier, its location.

Note: The table that follows is for illustrative purposes only.

Example of an Essential Principles Conformity Checklist

Essential Principle	Applicable to the device?	Method used to demonstrate conformity	Reference to Supporting Controlled Documents
General Essential Principles			
A1 IVD 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, and the medical and physical conditions of intended users, they will perform as intended by the manufacturer and 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>A2 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, and ▪ inform users of any residual risks. 			
A3 IVD medical devices should achieve the performance intended by the manufacturer and be designed, manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose.			
A4 The characteristics and performances referred to in Clauses A1, A2 and A3 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.			

Submission Dossier for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices
Work Group 2 AHWP/WG2/F003:2016

Essential Principle	Applicable to the device?	Method used to demonstrate conformity	Reference to Supporting Controlled Documents
A5 IVD medical devices should be designed, manufactured and packaged 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.			
A6 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			
C1 Chemical, physical and biological properties			
C1.1 The IVD medical devices should be designed and manufactured in such a way as to ensure the characteristics and performance referred to in Section 6 of the 'Essential Principles applicable to IVD Medical Devices'. Particular attention should be paid to the possibility of impairment of analytical performance due to incompatibility between the materials used and the specimens and/or analyte to be detected (such as biological tissues, cells, body fluids and micro-organisms), taking account of its intended purpose.			
C1.2 The IVD medical 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 device.			
C1.3 ----- etc. ----- -----			
C1.4 ----- etc. ----- -----			
C2.1			
C2.2			