Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

FINAL DOCUMENT

Title: AHWP Regulatory Framework for IVD Medical Devices

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1.0 Preface

The document herein was the effort of Asian Harmonization Working Party (AHWP) WG1a IVDD Subgroup. The 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. It contains the regulatory framework for IVD medical devices. This guidance is intended for both regulators and industry representatives.

2.0 Scope

The primary purpose of this document is to provide guidance for manufacturers of IVD medical devices, Regulatory Authorities (RA) and Conformity Assessment Bodies (CAB) in relation to coping with the challenges of establishing a regulatory framework for IVD medical devices. It contains recommendations for determining the pathway for regulatory approval for IVD medical devices in countries lacking of regulatory framework.

3.0 Introduction

This document has been developed to encourage and support global convergence of regulatory systems based on the AHWP guidance documents. It is intended for use by all key stakeholders including regulatory authorities, Conformity Assessment Bodies (CAB) and industry. The intent is that through an internationally harmonized regulatory framework, there would be benefits in establishing, in a consistent way, an economic and effective approach to assure the consistent safety, quality, and performance/effectiveness of medical devices in the interest of public health.

AHWP supports and encourages international regulatory harmonization but recognizes that regulatory authorities may have to consider their local needs when they introduce new IVD medical devices regulations based on their existing legal framework. However, regulatory authorities that are developing regulations for IVD medical devices, or amending existing ones, are encouraged to consider the adoption of the regulatory model mentioned in this document, or modify their current system as outlined in the this model, as this will help to reduce variations among systems world-wide and facilitate the process of international regulatory convergence.

4.0 References

GHTF/SG1/N29:2005 *Information Document Concerning the Definition of the Term 'Medical Device'.*

GHTF/SG1/N45:2007 *Principles of In Vitro Diagnostic Medical Devices Classification.*

GHTF/SG1/N46:2007 *Principles of Conformity Assessment for In Vitro Diagnostic Medical Devices.*

GHTF/SG1/N41:2005 *Essential Principles of Safety and Performance of Medical Devices.*

5.0 Definitions

- **Recognised Standard:** Standard deemed to offer the presumption of conformity to specific Essential Principles of safety and performance.
- **Technical Documentation:** The documented evidence, normally an output of the quality management system, which demonstrates conformity of a device to the *Essential Principles of Safety and Performance of Medical Devices*.

- **Conformity Assessment:** the systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the *Essential Principles of Safety and Performance of Medical Devices (SG1/N041).*

- **Technical Documentation:** the documented evidence, normally an output of the quality management system, that demonstrates compliance of a device to the *Essential Principles of Safety and Performance of Medical Devices (SG1/N041).*

- Diagnostic sensitivity (Clinical sensitivity): Ability of an IVD medical device to identify the presence of a target marker associated with a particular disease or condition.

  NOTE 1: Also defined as percent positivity in samples from subjects where the target disease or condition is known to be present.

  NOTE 2: Diagnostic sensitivity is a number fraction, calculated as true positive values divided by the sum of true positive plus false negative values.

  NOTE 3: The disease or condition is defined by criteria independent of the IVD medical device under consideration.

  Source: ISO 18113-1:2009 modified.

- Diagnostic specificity (Clinical Specificity): Ability of an IVD medical device to recognize the absence of a target marker associated with a particular disease or condition.

  NOTE 1: Also defined as percent negativity in samples where the target analyte (measurand) is known to be absent.

  NOTE 2: Diagnostic specificity is a number fraction, calculated as true negative values divided by the sum of true negative plus false positive values.

  NOTE 3: The disease or condition is defined by criteria independent of the medical device under consideration.

  Source: ISO 18113-1:2009 modified.

- Examination: Set of operations having the object of determining the value or characteristics of a property.

  NOTE 1: In some disciplines (e.g., microbiology) an examination is the total activity of a number of tests, observations or measurements.

  NOTE 2: Laboratory examinations that determine the value of a property are called quantitative examinations; those that determine the characteristics of a property are called qualitative examinations.

  NOTE 3: Laboratory examinations are also called 'assays' or 'tests.'

  Source: ISO 18113-1:2009 modified

- Predictive value: Probability that a person with a positive IVD medical device test result has a given condition under investigation, or that a person with a negative IVD medical device test result does not have a given condition.

  NOTE 1: The predictive value is determined by the diagnostic sensitivity and diagnostic specificity of the IVD medical device test procedure, and by the prevalence of the condition for which the examination is used.

  NOTE 2: Prevalence means the proportion of persons with a particular disease within a given population at a given time.

  NOTE 3: The positive predictive value indicates how effectively an IVD medical device separates true positive test results from false positive test results for a given attribute in a given population.

  NOTE 4: The negative predictive value indicates how effectively an IVD medical device separates true negative test results from false negative test results for a given attribute in a given population.

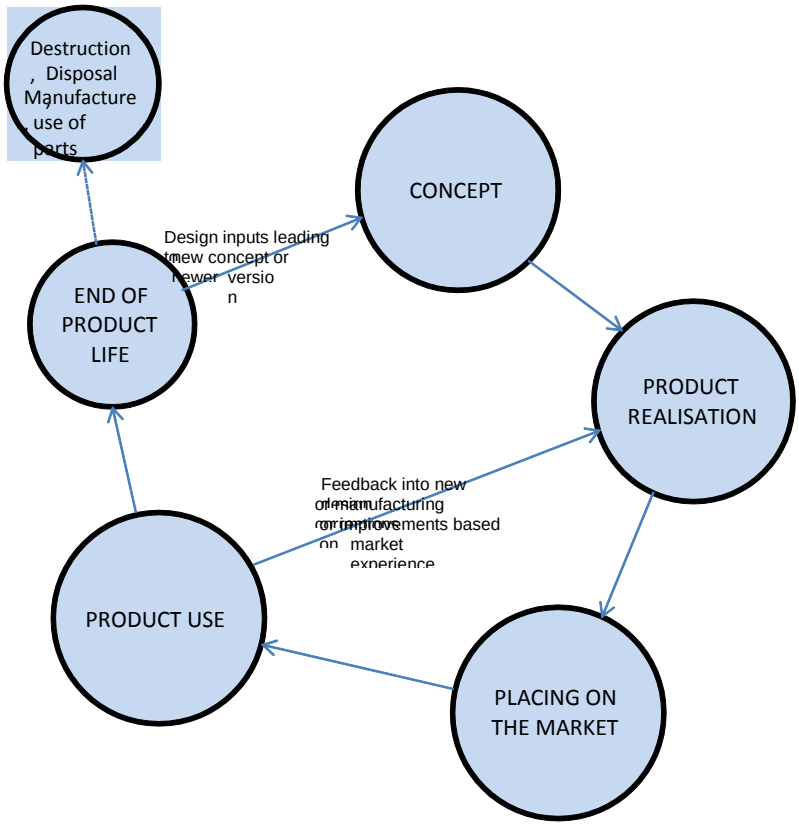
  Source: ISO 18113-1:2009 modified

6.0 How IVD Medical Devices are Regulated?

Most countries regulate medical devices, including IVD medical devices based on the Total-Product-Life-Cycle approach.

Figure 1 illustrates the fundamental life-cycle of a medical device. It demonstrates that medical device development is a continuous process from the initial concept of the device → to the various phases of product realization → to placing the device on the market → to marketing of the product through distribution, promotion, advertising, servicing → to obsolescence or renewal as a modified product. The figure also illustrates the fact that there are relationships among the phases of the life-cycle. For example, experience gathered in the marketing phase feeds back into the design and testing of new products, product improvements, or corrective actions.

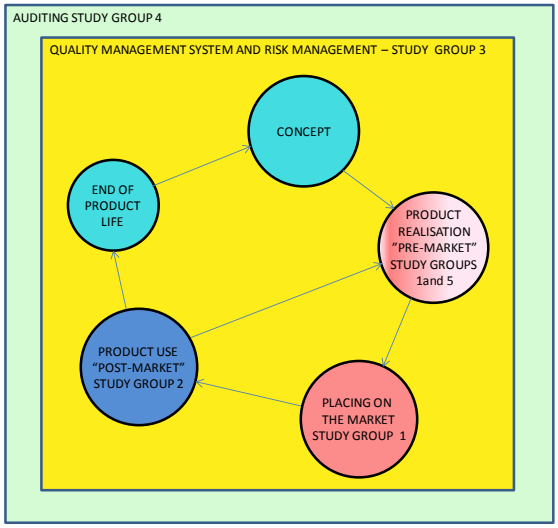
Figure 1: Fundamental Life Cycles of a Medical Device



Source: GHTF/AHWG-GRM/N1R13:2011

Figure 2 illustrates the application of regulatory processes to the product life-cycle. The entire cycle is subject to the regulatory processes of a Quality Management System (QMS), Risk Management, and Regulatory Auditing. Pre-market regulatory controls, such as Competent Authority or conformity assessment body review (valid in some jurisdictions) of summary technical files, may apply during product realization. The product is then supplied to the market subject to regulatory controls such as registration of the manufacturer. Post-market surveillance, vigilance controls and adverse event reporting apply during the marketing phase of the device.

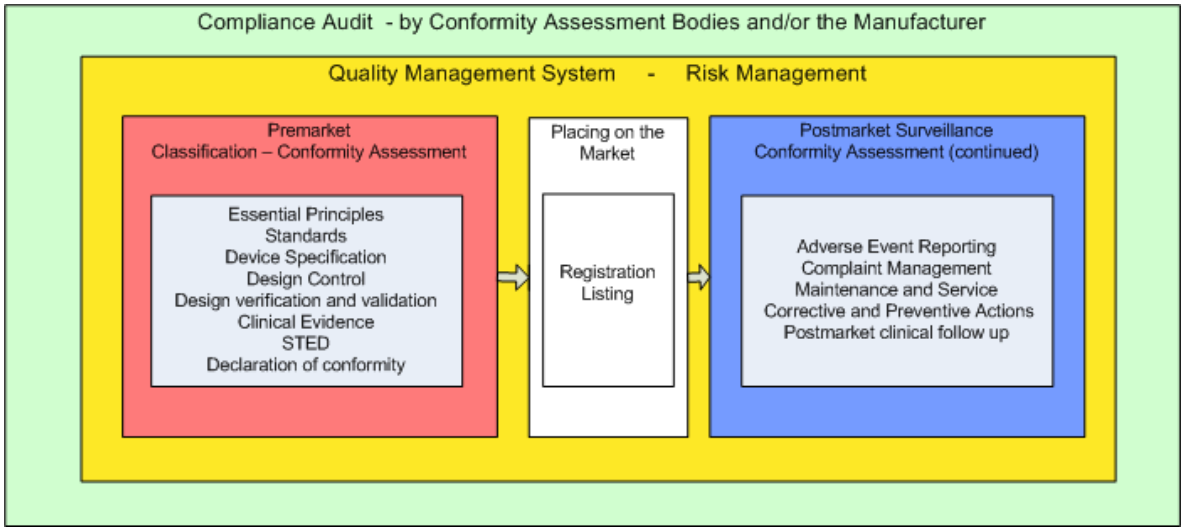
Figure 2: Application of Regulatory Processes to the Product Life Cycle



Source: GHTF/AHWG-GRM/N1R13:2011

Figure 3 displays the same information described in Figures 1 and 2, but in a linear representation. Here the regulatory model is displayed as three primary stages, including the Pre-market and Post-market stages. The regulatory activities within each stage are noted.

Figure 3: Product Life-Cycle, Linear Representation with Applied Processes



Source: GHTF/AHWG-GRM/N1R13:2011

It is highly recommended that the industry and regulators should continue working on finding a common ground for improving safety and efficacy of IVD medical devices. Furthermore, communication and cooperation among all stakeholders can benefit the patients, users and the environment.

7.0 Critical Path for Regulatory Approval of IVDs Medical Devices

Developing Conformity Assessment Process for IVD Medical Devices

Regulatory systems are intended to ensure a high level of protection of public health and safety. Public trust and confidence in IVD medical devices, and in the administrative systems by which they are regulated, are based on the safety and performance of such products throughout their life cycle.

Conformity assessment, conducted before and after an IVD medical device is placed on the market, and post-marketing surveillance of IVD medical devices in use are complementary elements of the Global Harmonization Task Force (GHTF) global regulatory model. (Refer to the following website for GHTF documents: http://www.imdrf.org/documents/documents.asp#ghtf) These complementary elements are

intended to provide the objective evidence of safety and performance, benefits and risks, to maintain public confidence.
Conformity assessment is primarily the responsibility of the IVD medical device manufacturer. However, it is done in the context of the established regulatory requirements and both the process and conclusions are subject to further review by the Regulatory Authority and/or Conformity Assessment Body.

In general, the degree of involvement of the Regulatory Authority or Conformity Assessment Body in such reviews is proportional to the risks associated with a particular category of devices.

The conformity assessment elements that the may include in a conformity assessment system are:

- a quality management system
- a system for post-market surveillance
- summary technical documentation
- a declaration of conformity
- the registration of manufacturers and their IVD medical devices by the Regulatory Authority.

All five elements are applicable to each of the device classes. Where there are alternatives within a conformity assessment element, the manufacturer may choose the one that it believes to be most suitable. The aforementioned elements describe the tasks of the manufacturer and, where appropriate, the responsibilities of the Regulatory Authority or Conformity Assessment Body.

By GHTF's definition, IVD medical device is a device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.

IVD medical devices can be classified according to the individual risk and public health risk. GHTF has proposed the following risk-based classification system:

CLASS	RISK LEVEL	DEVICE EXAMPLES
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyser , prepared selective culture media
B	Moderate Individual Risk and/or Low Public Health Risk	Vitamin B12, Pregnancy self testing, Anti-Nuclear Antibody, Urine test strips
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self testing, HLA typing, PSA screening, Rubella
D	High Individual Risk and High Public Health Risk	HIV Blood donor screening, HIV Blood diagnostic

Source: GHTF SG1-N45:2008

There are seven classification rules in accordance with the following principles:

- Intended use and indications for use as specified by the manufacturer
- Technical/scientific/medical expertise of the intended user
- The importance of the information to the diagnosis, taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a physician
- Impact of the result (true or false) to the individual and/or to public health

Refer to GHTF SG1-N45:2008 for further details on the classification rules.

After deciding the classification, the conformity of the device to the regulations should be assessed based on the following perspectives:

Conformity Assessment Element	Proposed Practice
Quality Management System	Establish QMS based on risk management
Post-Market Surveillance System	Integrate as part of the QMS
Registration of Manufacturers and Their Devices	*Utilize the Essential Principles and Recognized Standards*

Declaration of Conformity	Follow specific practice in each country
Technical Documentation	*Adopt IVD STED*

Refer to SG1-N46:2008 for further details.

By establishing a quality management system based on ISO 13485, a manufacturer might be able to ensure:

- a high degree of assurance (along with technical evaluation, where required in addition) that safe and effective devices will be available
- if satisfactory, results are evidence (or part thereof) of compliance with regulatory requirements necessary to market devices

GHTF consolidated best practices on medical device quality management system and regulatory audit in the following documents:

- GHTF SG3/N17:2008 *Guidance on Quality Management System*
- GHTF SG4/N28R4:2008 *Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers - Part 1: General Requirements*
- GHTF SG4/N30R20:2006 *Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy*
- GHTF SG4/N33R16:2007 *Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 3: Regulatory Audit Reports*
- GHTF SG4/N83:2010 *Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers Part 4: Multiple Site Auditing*
- GHTF SG4/N84:2010 *Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers Part 5: Audits of manufacturer control of suppliers*

A manufacturer of a medical device is expected to design and manufacture a product

that is safe and performs as intended. The fundamental design and manufacturing requirements are referred by the GHTF as 'Essential Principles of Safety and Performance'. There are six general requirements of safety and performance that apply to all medical devices and a comprehensive list of design and manufacturing requirements of safety and performance, some of which are relevant to each medical device.

The medical device manufacturer's design and manufacturing activities are under the control of its quality management system. Conformity of the device to all the applicable Essential Principles will be demonstrated and assessed according to procedures designated by the Regulatory Authority. The use of recognized standards gives presumption of conformity with relevant Essential Principles. The manufacturer is required to justify its decision to use particular standards through documented risk assessment, and take any risk mitigation action as appropriate.

The table below lists some of the related recognized standards used in demonstrating the safety and analytical performance of IVD medical devices:

Safety	**Recognized Standards**
Electrical Safety	IEC61010-1:2001
Electromagnetic Compatibility	IEC61326-2-6:2012
Software Verification, Validation and Testing	IEC62304:2006, IEC60601-1-4:2000, IEC60601-1-6:2010
Analytical Performance	**Recognized Standards**
Accuracy (trueness and precision)	CLSI EP5-A, CLSI EP12-A, CLSI EP15-A
Analytical sensitivity	CLSI EP12-A
Analytical specificity	CLSI EP7-A2
Linearity and measuring range	CLSI EP-6A
Limit of detection, limit of quantification of the method	CLSI EP-17A
Assay cut-off	CLSI GP10-A

Laboratory error, total analytical error	CLSI EP18-A, CLSI EP21-A
Stability	EN13640:2002
Interference	CLSI EP7-A2

Refer to GHTF SG1/N68:2012 and GHTF SG1/N44:2008 for further details

Apart from demonstrating conformity of the IVD medical device to the *Essential Principles of Safety and Performance of Medical Devices,* the manufacturer is expected to prepare and hold technical documentation that 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. This technical documentation is revised to reflect the current status of the IVD medical device through normal application of the manufacturer's QMS.

For the purpose of conformity assessment, the manufacturer consolidates the existing technical documentations into the format of STED (Summary Technical Documentation; as proposed by GHTF) or CSDT (Common Submission Dossier Template; as proposed by AHWP) to provide evidence to the Regulatory Authority/Conformity Assessment Body that the subject IVD medical device is in conformity with the Essential Principles. The STED/CSDT 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 Regulatory Authority for post-market purposes) and is prepared in order to meet regulatory requirements.

Where the STED/CSDT is submitted to a Regulatory Authority/Conformity Assessment Body, it should be in a language acceptable to the reviewing organization.

The depth and detail of the information contained in the STED/CSDT will primarily depend on the classification of the subject IVD medical device.

Refer to GHTF SG1/N63:2012 for further details on STED.

8.0 Clinical Evaluation Consideration for Affordable Access to IVD Medical Devices

The following GHTF documents provide useful advice on how to conduct clinical performance study for IVD medical devices:

- GHTF SG5/N6:2012 *Clinical Evidence for IVD Medical Devices-Key Definitions and Concepts*
- GHTF SG5/N7:2012 *Clinical Evidence for IVD Medical Devices-Scientific Validity Determination and Performance Evaluation*
- GHTF SG5/N8:2012 *Clinical Evidence for IVD Medical Devices-Scientific Validity Determination and Performance Evaluation*

To understand clinical evidence for IVD medical devices it must be taken into account that IVD medical devices differ from other medical devices in that the risks and benefits they pose are related to impact on patient management rather than direct contact between the device and the patient. A significant percentage of all healthcare decisions rely on information provided by clinical laboratory tests and these decisions can profoundly influence diagnosis and management of the patient.

Clinical evidence requirements will be influenced by the risk to the patient of an incorrect result from the IVD medical device, the degree of innovation reflected in the scientific/clinical recognition of the analyte of interest, the assay technology, the novelty, the degree of variability of the subject population and disease state, and the intended user(s) of the device. While not intended to impose unnecessary burdens, clinical evidence must support the intended use of the IVD medical device as stated by the manufacturer while addressing the relative risks to the patient associated with the use of the device.

Gathering of information to support clinical evidence starts at the research phase for IVD medical devices and this process consists of two major phases: the identification of the

scientific validity of the analyte and the performance evaluation of the specific IVD medical device.

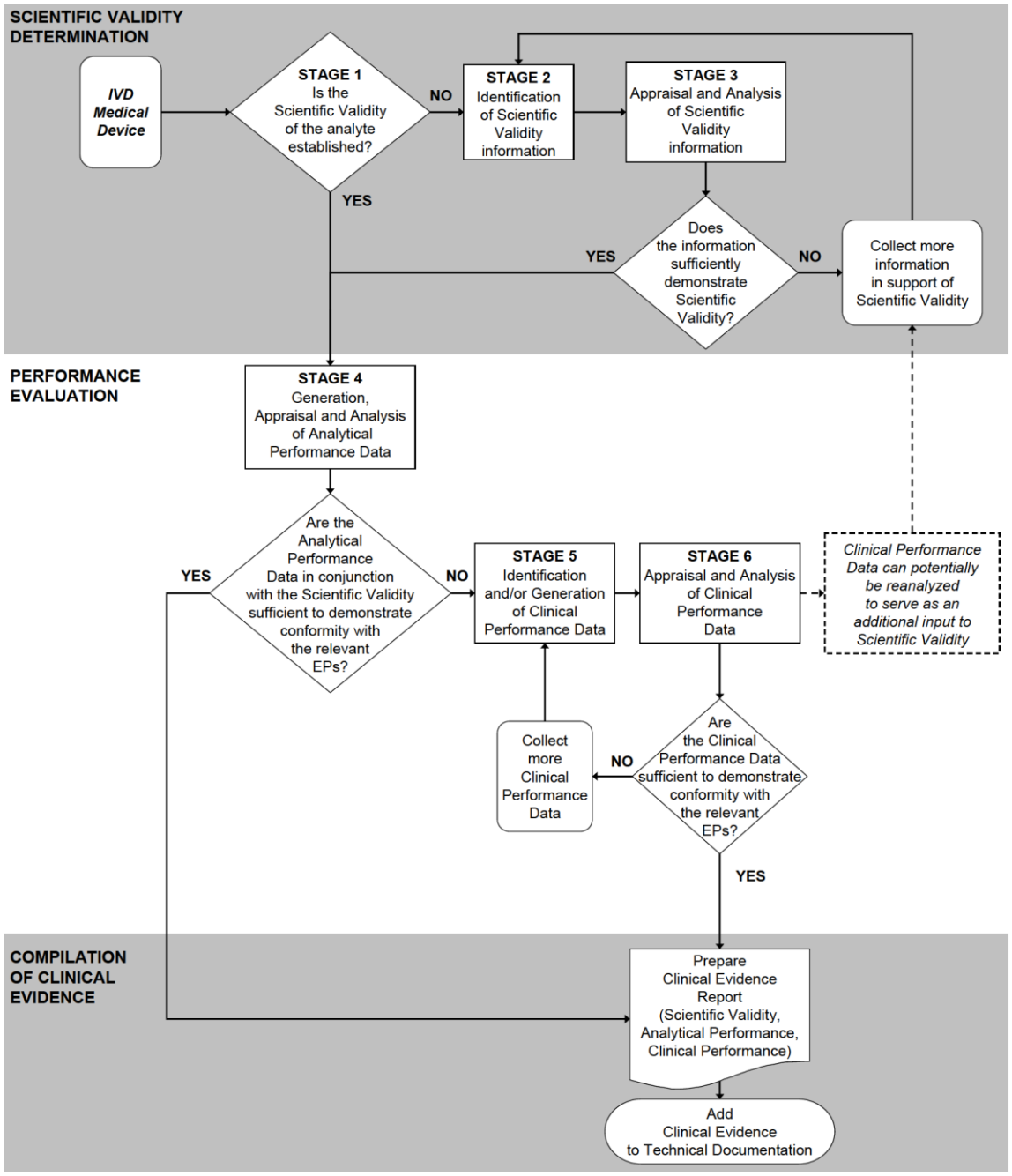
Once the scientific validity of an analyte is identified, the design process may lead to the development of an IVD medical device or a design change to an existing IVD medical device. The design process will be supported by a performance evaluation.

For IVD medical devices that have a new intended use, the existing clinical evidence report should be assessed as to its suitability to support the new intended use. If the new intended use is not supported by the existing evidence, then additions to the scientific validity, the analytical performance, and where appropriate, the clinical performance should be considered.

The generation and assessment of clinical evidence is an ongoing process. Information related to clinical evidence should be monitored routinely by the manufacturer once the IVD medical device is available on the market. Additional post-marketing information (e.g. adverse event reports, results from performance studies, published literature) should be reviewed as needed to determine possible impact on benefits and risks of the IVD medical device.

Figure 4 on the next page provides an overview of the stages involved in the assessment of clinical evidence.

Figure 4: Assessment of Clinical Evidence for IVD Medical Devices



Source: GHTF SG5/N6:2012

The following paragraphs describe the stages during the assessment of clinical evidence for IVD medical devices:

Stage 1 - Is the scientific validity of the analyte established?

Determination of scientific validity is not necessary where association of an analyte to a clinical condition/physiological state is well known, based on available information such as peer reviewed literature, textbooks, historical data and experience. For example it would not be reasonable to expect a manufacturer to demonstrate haemoglobin is associated with anaemia given the well established and recognized association. If the scientific validity is established, a brief rationale should be documented in the final clinical evidence report (e.g. a brief list of key references). Proceed to Stage 4.

For a new analyte and/or new intended use, scientific validity needs to be demonstrated. Proceed to Stage 2.

Stage 2 – Identification of scientific validity of the analyte

Potential sources for the identification of scientific validity information are:

- Information on IVD medical devices that measure the same analyte and with the same intended use that have marketing history (e.g. Instructions for Use)
- Literature searching: this information might be found in peer reviewed articles, regulatory guidance documents, conference proceedings, etc.
- Review of expert opinions: this information might be found in sources that include textbooks, clinical guidance documents, position statements from academic and professional organizations.
- Results from proof of concept studies: these studies are usually smaller scale scientific studies to identify the fundamental association of the analyte with the clinical condition/physiological state.
- Results from clinical performance studies

Scientific validity will be based on one or more of these potential information sources.

Stage 3 – Appraisal and analysis of scientific validity information

The purpose of the scientific validity appraisal is to select information based on its merits and limitations. Each piece of information is appraised to determine its relevance and quality for establishing the association between the analyte and the clinical condition/physiological state.

To be relevant the information source should reference both the analyte and the clinical condition/physiological state in question, and should show a clear link between the two.

The information provided should be of sufficient quality to enable a rational and objective assessment of the scientific validity.

The scientific validity analysis aims to collectively evaluate all of the appraised information, in terms of weight and significance.

The outcome of the analysis should include references, justifications and conclusions supporting a valid association between the analyte and the clinical condition/physiological state.

The scientific validity should be summarised as part of the clinical evidence report.