



PROPOSED DOCUMENT

Global Harmonization Task Force

Title: Clinical Evidence for IVD medical devices–Key Definitions and Concepts

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Preface

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide non-binding guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

There are no restrictions on the reproduction, distribution or use of this document; however, incorporation of this document, in part or in whole, into any other document, or its translation into languages other than English, does not convey or represent an endorsement of any kind by the Global Harmonization Task Force.

1.0 Introduction

GHTF would seek to evolve beyond convergence of regulatory requirements to embrace mutual acceptance of common data submissions, pre-market conformity assessment processes, quality systems, quality systems auditing results, and a broad sharing of post-marketing experience. The objective was to allow presentation of data that are acceptable in principle to relevant authorities as the basis for meeting regulatory requirements.

The broad goal for Study Group 5 is to promote the convergence of the regulatory requirements for the generation and presentation of evidence of the clinical safety and performance of medical devices. The Study Group 5 document SG5/N1R8 recognizes that, in order to progress convergence of regulatory requirements and acceptance of common data, it is necessary to have a common understanding and application of terminology, concepts and principles.

Taking into account the differences between medical devices other than IVD medical devices and IVD medical devices it was considered necessary to develop a document to specifically address the concepts, principles and terminology for clinical evidence related to IVD medical devices.

It is anticipated that convergence of requirements for clinical evidence, including common data submissions, will lead to better understanding of an IVD medical device's clinical utility and performance by all stakeholders, more efficient use of resources of the clinical community, medical device regulators and industry, and increased transparency and confidence in the global regulatory model. Ultimately, there should be more efficient, predictable and timely access to IVD medical devices by patients and society worldwide.

When placing an IVD medical device on the market the manufacturer must have demonstrated through the use of appropriate conformity assessment procedures that the device complies with the Essential Principles of Safety and Performance of Medical Devices. Generally, from a clinical perspective, it is expected that the manufacturer has demonstrated the device achieves its intended performance during normal conditions of use in the intended environment (e.g. blood-banks, hospitals, home environment). As IVD medical devices are used on specimens taken from the human body, the characteristics of clinical evidence are different from medical devices other than IVD medical devices.

2.0 Scope

This document is intended to:

- introduce the concepts and definitions of clinical evidence for IVD medical devices;
- examine the relationship between clinical evidence (scientific validity and performance), clinical utility and performance evaluation (analytical and clinical),
- serve as guidance to all those involved in the generation, compilation and review of clinical evidence sufficient to support the marketing of IVD medical devices (regulatory authorities, conformity assessment bodies, manufacturers of IVD medical devices and their associated industry groups).

NOTE : guidance about how to generate, compile and present clinical evidence for the purpose of demonstrating compliance with the Essential Principles of Safety and Performance of an IVD medical device will be described in a separate document.

3.0 References

SG1/N041:2005 *Essential Principles of Safety and Performance of Medical Devices*

SG1/N045:2008 *Principles of In Vitro Diagnostic (IVD) Medical Devices Classification*

SG1/N046:2008 *Principles of Conformity Assessment for IVD Medical Devices*

SG1/N063 *Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices*

SG5/NXXX *Clinical evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation*

4.0 Definitions and Concepts for IVD medical devices

NOTE : given the different characteristics of IVD medical devices these definitions might differ from the ones in the concept and definitions document SG5/N1R8 for medical devices.

4.1 Clinical evidence of an IVD medical device

Definition: Clinical evidence for an IVD medical device is all the information that supports the scientific validity and performance for its use as intended by the manufacturer.

Explanation: Clinical evidence is an important component of the technical documentation of an IVD medical device, which along with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the Essential Principles. It should be cross-referenced to other relevant parts of the technical documentation that impact its interpretation. The clinical evidence is used to support the marketing and labeling of the IVD medical device, including any claims made about the scientific validity and performance of the device.

Clinical evidence should be reviewed by the manufacturer when new

Information is obtained relating to :

- scientific validity (e.g from literature)
- clinical performance (e.g from post marketing experience).

NOTE: Scientific validity and clinical performance are common to both clinical evidence and clinical utility.

4.2 Scientific Validity of an analyte (measurand)

Definition: The association of an analyte (measurand) to a clinical condition/physiological state.

Explanation: Scientific validity is often identified in research, and is supported by studies evaluating the analyte (measurand) for potential clinical applications. Literature review and where applicable, feasibility and/or scientific studies will help to establish the potential scientific validity.

For many analytes (measurands) the scientific validity is well established. An example would be Calcium. The scientific validity for this analyte (measurand) is well established as being linked to the diagnosis and treatment of parathyroid disease, a variety of bone diseases, chronic renal disease and tetany.

However some IVD medical devices are developed when the scientific validity of the analyte (measurand) is still emerging. An example would be a newly characterized biomarker that is potentially useful in monitoring recurrence or progressive disease in patients with cancer.

As the scientific and medical knowledge further develops the initially established scientific validity might change and/or expand. An example of such evolving scientific validity would be CRP assays. These were initially established as being linked in the detection and evaluation of infection, tissue injury and inflammatory disorders. Subsequently CRP was found to be linked to the risk of cardiac disease if the sensitivity of the assay is appropriate for this clinical application.

4.3 Performance of an IVD medical device

Definition: The ability of an IVD medical device to achieve its intended purpose as claimed by the manufacturer. The performance of an IVD medical device consists of the analytical and, where applicable, the clinical performance supporting the intended use of the IVD medical device.

4.3.1 Analytical Performance

Definition: The ability of an IVD medical device to correctly detect or measure a particular analyte (measurand).

Explanation: The demonstration of analytical performance characteristics supports the intended use of the IVD medical device. These characteristics are determined by the collection of testing results from studies used to assess of the ability of the IVD medical device to measure a particular analyte (measurand). Such studies include, but are not limited to, analytical sensitivity, analytical specificity, accuracy (trueness and precision), linearity, limit of detection.

4.3.2 Clinical Performance

Definition: 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.

Explanation: The demonstration of clinical performance characteristics supports the intended use of the IVD medical device. Clinical performance characteristics are determined by the collection of testing results from studies used to demonstrate that the IVD medical device, depending on its diagnostic function, correctly identifies an individual's current or future state or correctly evaluates changes in an individual's state. Such studies include, but are not limited to, diagnostic sensitivity, diagnostic specificity based on the true disease status of the patient and negative and positive predictive values based on the prevalence of the disease.

NOTE : This term is sometimes referred to as clinical validity but clinical performance is the recommended term.

4.4 Performance evaluation of an IVD medical device

Definition: Assessment and analysis of data to establish or verify the performance of an IVD medical device.

Explanation: Performance evaluation for an IVD medical device is the investigation process by which generated data are assessed and analyzed to demonstrate the performance characteristics of the envisioned IVD medical device for the intended use as stated by the manufacturer. Data are typically generated from verification and validation studies (including where appropriate, clinical performance studies using human specimens) or obtained from literature review that confirm the performance characteristics of the product. This performance evaluation will support the demonstration of the conformity to the relevant essential principles of safety and performance.

4.5 Clinical Utility of the IVD medical device:

Definition: The usefulness of the results obtained from testing with the IVD medical device and the value of the information to the individual being tested and/or the broader population.

Explanation: Clinical utility of an IVD medical device supports clinical decisions for patient management such as effective treatment or preventive strategies. Clinical utility has been described as including many elements such as acceptability, appropriateness; availability of treatments/interventions, and health economics. Scientific validity and clinical performance are the only elements of clinical utility considered in this document because they are also components of clinical evidence. The manufacturer is expected to demonstrate clinical evidence for all IVD medical devices. Aside from scientific validity and clinical performance, a manufacturer is not required to demonstrate any other elements of clinical utility for premarket conformity assessment purposes.

4.6 Intended use / purpose:

Definition: The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.

Explanation: The intended use for an IVD medical device should also define the function or role of the IVD medical device such as diagnosis, aid to diagnosis, screening, physiological status, monitoring, predisposition, prognosis and prediction. These functions are important in determining the type and depth of clinical performance studies if applicable.

4.7 Relationship Between Clinical Evidence and Clinical Utility

The figure below shows how scientific validity and clinical performance are common elements of clinical evidence and clinical utility.

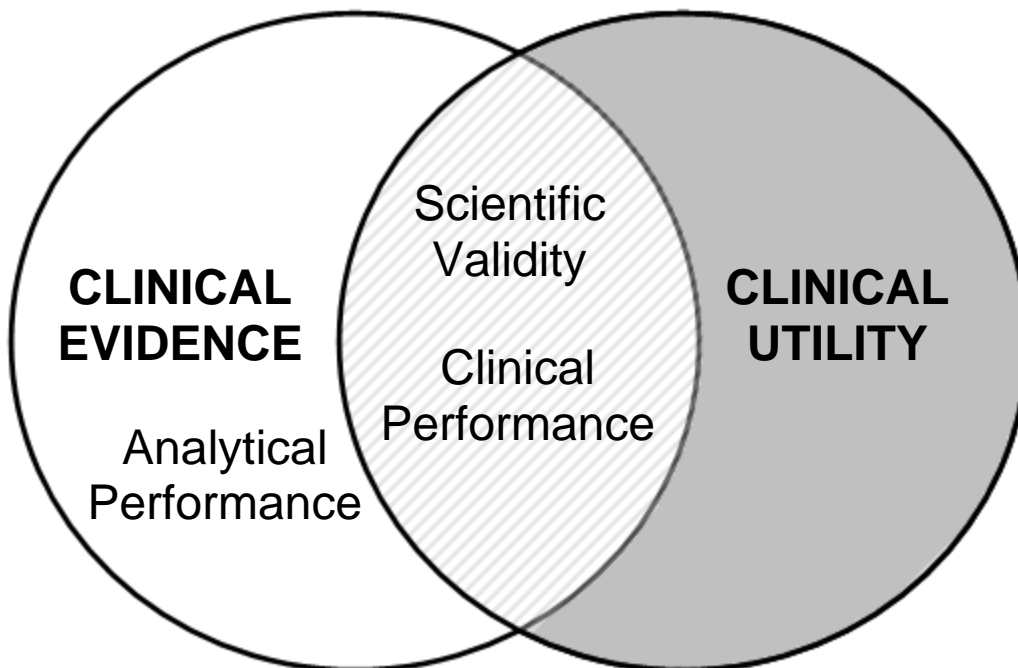


Figure 1: Relationship between Clinical Evidence and Clinical Utility

The following is an example (HBV genotype test) that illustrates the concepts defined in this document:

Scientific validity :

Has the mutation been described in a clinical setting?

Is the mutation associated with drug resistance?

Analytical performance :

Does the IVD medical device detect the mutation?

Clinical performance :

Does the IVD medical device detect the mutation in the appropriate population?

Clinical Utility :

Does the patient benefit from the information obtained with the IVD medical device (e.g. treatment modification)?