



FINAL DOCUMENT

Global Harmonization Task Force

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

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This document was produced by the Global Harmonization Task Force, a voluntary international group of representatives from medical device regulatory authorities and trade associations from Europe, the United States of America (USA), Canada, Japan and Australia.

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

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Preface

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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 IVD medical devices and other 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 scientific validity 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 GHTF's Essential Principles of Safety and Performance of Medical Devices (EPs). Generally, from a clinical evidence 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. laboratories, physician's offices, healthcare centers, home environments) and in the intended use population. As IVD medical devices are used for the examination of specimens derived 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, analytical performance and, where applicable, clinical performance) and clinical utility;

- 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 (RA), Conformity Assessment Bodies (CAB), manufacturers of IVD medical devices and their associated industry groups).

NOTE: This document should not be used in isolation but read together with the documents ‘*Clinical evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation and Clinical evidence for IVD medical devices*’ and ‘*Clinical evidence for IVD medical devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices*’ as well as the document ‘*Essential Principles of Safety and Performance of Medical Devices*’ and the document ‘*Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices*’ (references provided in the reference section).

3.0 References

GHTF/SG1/N068:2012 *Essential Principles of Safety and Performance of Medical Devices*

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

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

GHTF/SG1/N063:2011 *Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices*

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 – Clinical Performance Studies for In Vitro Diagnostic Medical Devices*

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 IVD medical device

Refer to GHTF/SG1/N71:2012 *Definition of the Terms ‘Medical Device’ and ‘In Vitro Diagnostic (IVD) Medical Device’*

4.2 Clinical Evidence for 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.

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.

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.

NOTE: Scientific validity and clinical performance are common to both clinical evidence and clinical utility (refer to Figure 1).

4.3 Scientific Validity of an Analyte

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

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

For many analytes, the scientific validity is well established. An example would be calcium in serum. The scientific validity for this analyte 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 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 C-reactive protein (CRP). This analyte was 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 performance of the assay is appropriate for this clinical application.

4.4 Performance of an IVD medical device

Definition: The ability of an IVD medical device to achieve its intended use 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.

4.4.1 Analytical Performance

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

Explanation: The demonstration of analytical performance supports the intended use of the IVD medical device. Analytical performance is determined by the collection of testing results (analytical performance data) from analytical performance studies used to assess the ability of the IVD medical device to measure a particular analyte. Analytical performance may include analytical sensitivity (e.g. limit of detection), analytical specificity (e.g. interference, cross-reactivity), accuracy (derived from trueness and precision), and linearity.

4.4.2 Clinical Performance of an IVD medical device

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 supports the intended use of the IVD medical device. Clinical performance demonstrates that the IVD medical device, depending on its test purpose, identifies an individual's current or future state or evaluates changes in an individual's state. Clinical performance may include expected values, diagnostic sensitivity and diagnostic specificity based on the known clinical/physiological state of the individual, and negative and positive predictive values based on the prevalence of the disease.

Clinical performance data can be derived from multiple sources such as clinical performance studies, literature, or experience gained by routine diagnostic testing.

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

4.5 Clinical Performance Study

Definition: A study undertaken to establish or confirm the clinical performance of an IVD medical device.

Explanation: The purpose of a clinical performance study is to establish or confirm aspects of IVD medical device performance which cannot be determined by analytical performance studies, literature and/or previous experience gained by routine diagnostic testing. This information is used to demonstrate compliance with the relevant Essential Principles with respect to clinical performance. Clinical performance studies include those conducted for the purpose of gaining market approval, as well as those conducted following market approval.

For further information, refer to SG5/N8 *Clinical evidence for IVD medical devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices*.

NOTE: This term is synonymous with ‘clinical trial’ and ‘clinical study’.

4.6 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 data are assessed and analyzed to demonstrate the performance 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 reviews that confirm the performance of the product. The performance evaluation supports the demonstration of the conformity to the relevant essential principles of safety and performance.

4.7 Clinical Utility of an 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. (refer to Figure 1)

4.8 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 IVD medical device test purpose such as diagnosis, aid to diagnosis, screening, , monitoring, predisposition, prognosis, prediction, and physiological status determination. Other relevant aspects include the specific disorder, condition or risk factor of interest, the testing population and, where applicable, the intended user.

This information will determine the type and depth of the clinical evidence – refer to SG5/N7 *Clinical evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation* and SG5/N8 *Clinical evidence for IVD medical devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices*.

For more details on intended use/purpose for IVD medical devices refer to SG1/N063 *Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices*.

4.9 Relationship between Clinical Evidence and Clinical Utility

The clinical evidence is a compilation of the scientific validity, analytical performance and, where applicable, clinical performance.

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

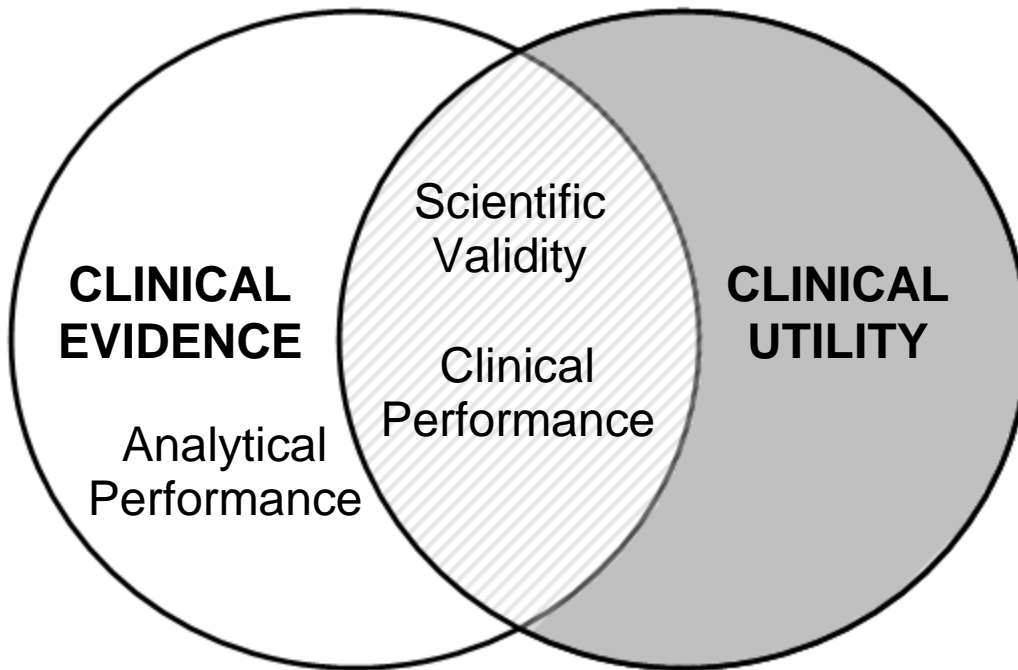


Figure 1: Relationship between Clinical Evidence and Clinical Utility

4.10 Illustrative Example of Clinical Evidence Concepts

The following is an example that illustrates the concepts defined in this document. In this example, a genotype test was developed to detect a recently-observed HBV mutation. The intended use of IVD medical device by the manufacturer is to determine the likelihood of treatment failure associated with this mutation.

Scientific validity

Scientific validity in this example refers to the association of the HBV mutation with a particular clinical state.

Potential questions:

Has the mutation been described in a clinical setting?

Is the mutation associated with drug resistance?

Is the mutation associated with a worse clinical outcome?

Analytical performance

Analytical performance in this example refers to the ability of the genotype test to detect the HBV mutation.

Potential question:

Does the genotype test identify the HBV mutation (in spiked or native specimens)?

Clinical performance

Clinical performance in this example refers to the ability of the genotype test to detect the HBV mutation in the intended use population.

Potential questions:

Does the genotype test identify the mutation in patient specimens from which the HBV mutant has been isolated?

How well do the testing results of the HBV genotype test correlate with treatment failure in the intended use population?

Clinical utility

Clinical utility in this example refers to whether or not patients benefit from the information obtained with the genotype test.

Potential questions:

Are treatments available to effectively manage patients infected with the HBV mutant?

What is the likelihood that the test results will lead to an improved patient outcome (e.g. treatment modification)?