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# In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples

*Dispositifs médicaux de diagnostic in vitro — Exigences pour l'établissement d'une traçabilité métrologique des valeurs attribuées aux étalons, aux matériaux de contrôle de la justesse et aux échantillons humains*

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# Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*.

This second edition cancels and replaces the first edition (ISO 17511:2003), which has been technically revised. The main changes compared to the previous edition are as follows:

— incorporation of the special requirements for metrologically traceable calibration hierarchies for measurement of catalytic concentration of enzymes (previously covered in ISO 18153:2003);

— to clarify that final reported values on human samples shall be metrologically traceable to the highest order available reference, the title and scope were modified to include metrological traceability of values assigned to human samples;

— updated normative references to remove International Vocabulary of Basic and General Terms in Metrology, 2nd edition, ISO, Geneva (1993) and ISO Guide 35:1989, Certification of reference materials — General and statistical principles;

— revision of Clause 4 to clearly define requirements of a manufacturer of an in vitro diagnostic medical device in establishing and documenting metrological traceability of assigned values (for calibrators, trueness controls and human samples), while incorporating requirements previously addressed in Clauses 6, 7 and 8 (thus eliminating those sections);

— revision of Clause 5 to incorporate additional models of metrologically traceable calibration hierarchies, especially 5.3 for measurement of catalytic concentration of enzymes (where the measurand is defined by a primary RMP; previously addressed in ISO 18153:2003), and 5.6 for an overview of the concept of assigned values of materials for measurands with metrological traceability to international harmonisation protocols (addressed in detail in ISO 21151).

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.


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# Introduction

In laboratory medicine, the objective of examining a measurand in a human sample is to produce laboratory results that will enable a clinician to assess the risk of a disease, or to diagnose and make treatment decisions for a medical condition. To be clinically useful, the results obtained from a given human sample examined by different laboratories or among different in vitro diagnostic medical devices (IVD MDs) within a single laboratory should be equivalent, regardless of the measurement procedure employed. Equivalent results allow uniform application of medical decision limits and reference intervals, which can reduce the risk of harm caused by medical decisions based on non-equivalent examination results. Equivalence of results among different IVD MDs for the same measurand is also important for the analysis of results in medical records for the purpose of supporting clinical decisions and for conducting epidemiological investigations.

Equivalent results for human samples for a measurand can be achieved by establishing metrological traceability of the values assigned to the calibrators for a measurement procedure (MP) to the highest available reference system component for the measurand. Metrological traceability describes the calibration hierarchy and the sequence of value assignments, demonstrating an unbroken linkage between the measurement result for a human sample up to the highest available reference system component in the calibration hierarchy. The point at which metrological traceability begins (i.e. the highest level of metrological traceability in the calibration hierarchy) depends on the availability of higher order reference measurement procedures (RMPs), reference materials (RMs) or harmonisation protocols for the stated measurand.

Limitations in implementing metrologically traceable calibrations occur when different IVD MDs intended for the same measurand do not measure the same or very closely related measurable quantities. Some measurands of medical interest may be well-defined elements or molecules. An increasing number of medical decisions depend on measurands that consist of complex and variable mixtures of chemical structures, molecular species and molecular complexes in varying proportions, e.g. glycoproteins with multiple isoforms, variant amino acid sequences, nucleic acid sequences, and other complex molecular forms. When the selectivity of an IVD MD is not fit-for-purpose, sample-specific influence quantities in human samples due to factors including disease, drugs or other pathological conditions may lead to erroneous values for the intended measured quantity. Even with metrological traceability to higher order reference system components, the selectivity of MPs at all levels in the calibration hierarchy for a given IVD MD can influence its ability to achieve results for human samples that are equivalent to the results obtained with other IVD MDs for the same measurand.

This document presents requirements for manufacturers of IVD MDs in documenting the calibration hierarchy for a measured quantity in human samples using a specified IVD MD. The document includes various model calibration hierarchies offering potential technical solutions for different kinds of measurands in establishing metrological traceability of assigned values for human samples, calibrators and trueness control materials. Use of this document as part of a broadly-based risk management program for manufacturers of IVD MDs is consistent with the requirements of ISO 14971 and is expected to assist in the reduction of the risk of harm to patients due to non-equivalence of results among different IVD MDs.


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# In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples

## 1 Scope

This document specifies technical requirements and documentation necessary to establish metrological traceability of values assigned to calibrators, trueness control materials and human samples for quantities measured by IVD MDs. The human samples are those intended to be measured, as specified for each IVD MD. Metrological traceability of values for quantities in human samples extends to the highest available reference system component, ideally to RMPs and certified reference materials (CRMs).

All parties having a role in any of the steps described in a calibration hierarchy for an IVD MD are subject to the requirements described. These parties include but are not limited to manufacturers (of IVD MDs), RMP developers (see ISO 15193), RM producers (see ISO 15194), and reference/calibration laboratories (see ISO 15195) supporting calibration hierarchies for IVD MDs.

NOTE 1 Producers of RMs intended for use in standardization or calibration of IVD MDs include commercial and non-commercial organizations producing RMs for use by many end-users of IVD MDs and/or calibration laboratories, or for use by a single end-user medical laboratory, as in the case of a measurement standard (calibrator) intended to be used exclusively for calibration of a laboratory-developed MP.

This document is applicable to:

a) all IVD MDs that provide measurement results in the form of numeric values, i.e. rational (ratio) and/or differential (interval) scales, and counting scales.

b) IVD MDs where the measurement result is reported as a qualitative value established with a ratio of two measurements (i.e. the signal from a specimen being tested and the signal from a RM with a specified concentration or activity at the cut-off), or a counting scale, with corresponding decision threshold(s). This also includes IVD MDs where results are categorized among ordinal categories based on pre-established quantitative intervals for a quantity.

c) RMs intended for use as trueness control materials for verification or assessment of calibration of IVD MDs, i.e. some commutable CRMs and some external quality assessment (EQA) materials (if so indicated in the RM's intended use statement).

d) IVD MD-specific calibrators and trueness control materials with assigned values, intended to be used together with a specified IVD MD.

e) IVD MDs as described in a) and b), where no end-user performed calibration is required (i.e. when the manufacturer performs a factory calibration of the IVD MD).

This document is not applicable to:

a) calibrators and trueness control materials for IVD MDs which, due to their formulation, are known to have zero amount of measurand;

b) control materials that are used only for internal quality control purposes in medical laboratories to assess the imprecision of an IVD MD, either its repeatability or reproducibility, and/or for assessing changes in IVD MD results compared to a previously established calibration condition;

c) control materials that are used only for internal quality control purposes in medical laboratories and which are supplied with intervals of suggested acceptable values that are not metrologically traceable to higher order reference system components;

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d) properties reported as nominal scales and ordinal scales, where no magnitude is involved.

NOTE 2 Nominal scales are typically used to report e.g. identity of blood cell types, microorganism types, identity of nucleic acid sequences, identity of urine particles.

NOTE 3 Ordinal scales are often applied to results differentiated into dichotomous groupings (e.g. 'sick' vs. 'healthy'), and occasionally to results differentiated into non-dichotomous categories where the result categories are rank-ordered but the rank-ordered categories cannot be differentiated in terms of relative degree of difference, e.g. negative, +1, +2, +3 for grading of presence of haemoglobin in urine specimens by visual observation.

## 2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 18113-2, *In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 2: In vitro diagnostic reagents for professional use*

ISO 15193, *In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Requirements for content and presentation of reference measurement procedures*

ISO 15194, *In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Requirements for certified reference materials and the content of supporting documentation*

## 3 Terms and definitions, symbols and abbreviated terms

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

**3.1**
**analyte**
component represented in the name of a measurable *quantity* (3.38)

EXAMPLE In the type of *quantity* (3.38) "mass of protein in 24-hour urine", "protein" is the analyte. In "amount of substance of glucose in plasma", "glucose" is the analyte. In both cases the long phrase represents the *measurand* (3.26).

**3.2**
**analytical selectivity**
**selectivity of a measuring system**
**selectivity**
property of a *measuring system* (3.29), used with a specified *MP* (3.27), whereby it provides measured *quantity* (3.38) values for one or more *measurands* (3.26) such that the values of each *measurand* (3.26) are independent of other *measurands* (3.26) or other *quantities* (3.38) in the phenomenon, body, or substance being investigated

EXAMPLE Capability of a *measuring system* (3.29) to measure the amount-of-substance concentration of creatinine in blood plasma without being influenced by the other components present in the sample.

Note 1 to entry: In chemistry, selectivity of a *measuring system* (3.29) is usually obtained for *quantities* (3.38) with selected components in concentrations within stated intervals.

Note 2 to entry: Selectivity as used in physics is a concept close to specificity as it is sometimes used in chemistry.


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