INTERNATIONAL STANDARD

ISO 17511

Second edition
2020-04

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

Reference number
ISO 17511:2020(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

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.

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.

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;

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.

[SOURCE: ISO/IEC Guide 99:2007 4.13, modified — 'analytical selectivity' added as the preferred term. Included only Example 5 with abbreviated text and NOTES 3 and 4.]

3.3
measurement bias
bias
estimate of a systematic measurement error

Note 1 to entry: See ISO/IEC Guide 99:2007 2.17, systematic measurement error.

Note 2 to entry: This definition applies to quantitative measurements only.

[SOURCE: ISO/IEC Guide 99:2007 2.18, modified — Note 1 and 2 to entry have been added.]

3.4
calibration
operation that, under specified conditions, in a first step, establishes a relation between the *quantity* (3.38) values with *measurement uncertainties* (3.48) provided by *measurement standards* (3.28) and corresponding indications with associated *measurement uncertainties* (3.48) and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication

Note 1 to entry: A calibration may be expressed by a statement, calibration function, calibration diagram, calibration curve, or calibration table. In some cases, it may consist of an additive or multiplicative correction of the indication with associated *measurement uncertainty* (3.48).

Note 2 to entry: Calibration should not be confused with adjustment of a *measuring system* (3.29), often mistakenly called "self-calibration", or with *verification* (3.50) of calibration.

Note 3 to entry: Often, the first step alone in the above definition is perceived as being calibration.

[SOURCE: ISO/IEC Guide 99:2007 2.39]

3.5
calibration hierarchy
sequence of *calibrations* (3.4) from a reference to the final *measuring system* (3.29), where the outcome of each *calibration* (3.4) depends on the outcome of the previous *calibration* (3.4)

Note 1 to entry: *Measurement uncertainty* (3.48) necessarily increases along the sequence of *calibrations* (3.4).

Note 2 to entry: The elements of a calibration hierarchy are one or more *measurement standards* (3.28) and *measuring systems* (3.29) operated according to *MPs* (3.27).

Note 3 to entry: A comparison between two *measurement standards* (3.28) may be viewed as a *calibration* (3.4) if the comparison is used to check and, if necessary, correct the *quantity* (3.38) value and *measurement uncertainty* (3.48) attributed to one of the *measurement standards* (3.28).

Note 4 to entry: In this document, a calibration hierarchy is defined as a detailed description of the process for assigning a value of a *measurand* (3.26) to a sample using a specified sequence of *MPs* (3.27) and *RMs* (3.39) (calibrated by higher order *RMs* (3.39) and/or *MPs* (3.27) for the same type of *quantity* (3.38), where available).

Note 5 to entry: For purposes of this definition, a sample includes human samples as well as *calibration materials* (3.6), EQA materials or other *RMs* (3.39).

[SOURCE: ISO/IEC Guide 99:2007 2.40, modified — excludes original Note 3. Note 3 to entry is Note 4 and Note 5 has been added.]

3.6
calibrator
calibration material
measurement standard (3.28) used in *calibration* (3.4) of a *measuring system* (3.29) according to a specified *MP* (3.27)

[SOURCE: ISO/IEC Guide 99:2007 5.12, modified — “calibration material” has been added as an admitted term, "of a measuring system according to a specified MP" has been added at the end of the definition, NOTE has been deleted.]

3.7
catalytic activity
property of a component corresponding to the catalysed substance rate of conversion of a specified chemical reaction, in a specified *measuring system* (3.29)

Note 1 to entry: In this document the "component" is an enzyme.

Note 2 to entry: The *quantity* (3.38) "catalytic activity" relates to an amount of active enzyme, not its concentration; see 3.8.

Note 3 to entry: The coherent derived SI unit is "katal" (kat), equal to "mole per second" (mol s^{-1}).

Note 4 to entry: The *MP* (3.27) is an essential element of the definition of the *measurand* (3.26).

Note 5 to entry: In many instances, instead of the conversion rate of the substrate ascribed in the short name of the enzyme *analyte* (3.1), e.g. "creatine" in "creatine kinase", the conversion rate of an indicator substance as substrate of a combined reaction is measured. Then the *measurand* (3.26) should be defined as 'catalytic activity of the enzyme as measured by the conversion rate of an indicator substance in a specified system according to a given *MP* (3.27)', e.g. 'catalytic activity of creatine kinase as measured by the rate of conversion of NADP+ in the IFCC reference procedure in human serum'.

[SOURCE: ISO 18153:2003, 3.2]

3.8
catalytic-activity concentration
catalytic concentration
catalytic activity (3.7) of a component divided by volume of the original system

Note 1 to entry: The coherent derived SI unit is "katal per cubic metre" or "mole per second cubic metre" (kat m^{-3} = mol s^{-1} m^{-3}). In laboratory medicine, the unit of volume can be chosen to be "litre" (L).

Note 2 to entry: In this document the "component" is an enzyme and the "original system" can be, for example, the plasma of a blood sample.

[SOURCE: ISO 18153:2003, 3.3]

3.9
certified reference material
CRM
RM (3.39) accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated *uncertainties* (3.48) and *traceabilities* (3.31), using valid procedures

EXAMPLE Human serum with assigned *quantity* (3.38) value for the concentration of cholesterol and associated *measurement uncertainty* (3.48) stated in an accompanying certificate, used as a *calibrator* (3.6) or measurement *trueness control material* (3.46).

Note 1 to entry: ‘Documentation’ is given in the form of a ‘certificate’ (see ISO Guide 31).

Note 2 to entry: Procedures for the production and CRM certification are given in ISO 17034:2016 and ISO Guide 35:2017.

Note 3 to entry: In this definition, "uncertainty" covers both '*measurement uncertainty*' (3.48) and 'uncertainty associated with the value of a nominal property', such as for identity and sequence. "Traceability" covers both '*metrological traceability* (3.31) of a quantity value' and 'traceability of a nominal property value'.

Note 4 to entry: Specified *quantity* (3.38) values of CRMs require *metrological traceability* (3.31) with associated *measurement uncertainty* (3.48)[25].

Note 5 to entry: ISO/REMCO has an analogous definition[25] but uses the modifiers "metrological" and "metrologically" to refer to both *quantities* (3.38) and nominal properties.

Note 6 to entry: Specific requirements for CRMs and the content of supporting documentation (in the field of in vitro diagnostic medical devices) are given in ISO 15194.

Note 7 to entry: For a specified material, a *calibration* (3.4) certificate provided by an accredited *calibration* (3.4) laboratory does not confer the status of CRM on these types of materials.

[SOURCE: ISO/IEC Guide 99:2007 5.14, modified — Note 6 and 7 to entry have been added.]

3.10
commutability of a reference material
commutability
property of a *RM* (3.39), demonstrated by the closeness of agreement between the relation among the measurement results for a stated *quantity* (3.38) in this material, obtained according to two *MPs* (3.27), and the relation obtained among the measurement results for other specified materials

Note 1 to entry: The *RM* (3.39) in question is usually a *calibrator* (3.6) and the other specified materials are usually routine samples.

Note 2 to entry: In commutability assessment of an *RM* (3.39), comparisons among all applicable *MPs* (3.27) is desirable.

Note 3 to entry: Closeness of agreement of measurement results is defined in terms of fitness for purpose as appropriate for the intended use of the *RM* (3.39).

Note 4 to entry: A commutability statement is restricted to the *MPs* (3.27) as specified in a particular comparison.

[SOURCE: ISO/IEC Guide 99:2007 5.15 modified — Note 2 and Note 3 have been deleted. Note 2 to entry to Note 4 to entry have been added.]

3.11
control material
substance, material or article intended by its *manufacturer* (3.22) to be used to verify the performance characteristics of an *IVD MD* (3.21)

[SOURCE: ISO 18113-1:2009, 3.13]

3.12
end-user IVD MD calibrator
end-user calibrator
RM (3.39) used as a *measurement standard* (3.28) intended for use with one or more *IVD MD* (3.21) *MPs* (3.27) intended to examine a particular *measurand* (3.26) in human samples

Note 1 to entry: End user calibrators includes *RMs* (3.39) or *calibrators* (3.6) applied internally by the *manufacturer* (3.22) to implement a final *calibration* (3.4) of the *IVD MD* (3.21), prior to the *IVD MD's* (3.21) release and delivery to the end-user, where end-user calibration is not required (i.e. 'factory calibration').

Note 2 to entry: Factory-generated *calibrations* (3.4) or *calibration* (3.4) functions include *calibration* (3.4) information (equations, formula, functions, parameters, data) stored, e.g., in electronic format, for use with a microprocessor as part of an *IVD MD* (3.21) *measuring system* (3.29) to transform "signal" generated in the course of measuring unknown human samples to an amount of substance or other final measured value.

3.13
equivalence of measured values
equivalent results
agreement of measured values among different *IVD MDs* (3.21) intended to measure the same *measurand* (3.26), where the differences in measured values on the same human samples do not affect clinical interpretation

Note 1 to entry: A conclusion of equivalence of measured values for the same human samples among two or more *MPs* (3.27) is based on the differences in measured values being within a pre-defined margin or limit.

[SOURCE: Harmonization.net, modified — wording revised for clarity.]

3.14
higher order reference material
higher order RM
CRM (3.9) that meets internationally accepted quality requirement and provides a common metrological reference within the *calibration hierarchy* (3.5) to which *manufacturers* (3.22) can establish *metrological traceability* (3.31)

Note 1 to entry: Quality requirements for higher order RMs are laid out in ISO 15194.

Note 2 to entry: Higher order RMs include fit–for–purpose *primary RMs* (3.35), *primary calibrators* (3.37), *secondary calibrators* (3.42) and *international conventional calibrators* (3.17).

Note 3 to entry: Pure substances constitute the *primary measurement standard* (3.37) and ultimate source of higher-order *metrological traceability* (3.31) for most traceability chains in chemistry, thermometry and calorimetry in general and for the certification of solution and *matrix* (3.24) *RMs* (3.39) in particular (see ISO Guide 35:2017).

Note 4 to entry: According to Joint Committee for Traceability in Laboratory Medicine (JCTLM) FAQs[27], a higher order RM is a *CRM* (3.9), meeting internationally accepted quality requirements, to which other measurement results can be referenced, and its *measurement uncertainty* (3.48) is completely established. Metrologically, a higher order RM is a *RM* (3.39) deployed at a higher level in the *calibration hierarchy* (3.5). Certified, highest order RMs, where available, are used by *IVD MD* (3.21) *manufacturers* (3.22) to assign values to *working calibrators* (3.51). These *working calibrators* (3.51) are subsequently used by the *manufacturer* (3.22) to assign values to *measurands* (3.26) in *end-user IVD MD calibrators* (3.12) and *control materials* (3.11) for use with *IVD MDs* (3.21) in medical laboratories and other IVD testing environments. Higher order RMs are most commonly produced and distributed by national metrology institutes (NMIs), e.g. U.S. National Institute of Standards and Technology (NIST), European Commission Joint Research Centre (EU-JRC), LGC Standards (UK), World Health Organization (WHO), National Institute for Biological Standards and Control (UK), National Institute of Metrology (CN), National Metrology Institute of Japan (JP), Reference Material Institute for Clinical Chemistry Standards (JP), Japanese Industrial Standards Committee (JISC), Centro Nacional de Metrología (MX), etc. Some commercial sources also provide RMs listed by JCTLM[28].

3.15
higher order reference measurement procedure
higher order RMP
reference measurement procedure (RMP) (3.40) meeting internationally accepted quality requirements and providing a common metrological reference within the *calibration hierarchy* (3.5) to which *manufacturers'* (3.22) can establish *metrological traceability* (3.31) and accepted as providing measurement results fit for their intended use in assessing *measurement trueness* (3.47)

Note 1 to entry: Quality requirements for *higher order RMPs* (3.15) are defined in ISO 15193.

Note 2 to entry: For reasons of higher cost, equipment complexity and operator training requirements, higher order RMPs are typically performed in national *metrology* (3.32) institutes and/or accredited *calibration* (3.4) laboratories.

Note 3 to entry: In laboratory medicine, *RMPs* (3.40) that meet the requirements of ISO 15193 are considered to be higher order RMPs.

Note 4 to entry: According to JCTLM FAQs[27], higher order RMPs are well documented, high accuracy *(MPs)* (3.27) used for assigning values to *calibration materials* (3.6). At the highest level (these *MPs*) (3.27) are frequently expensive to develop, too complicated for routine use and not suitable for high throughput analysis.

3.16
influence quantity
quantity (3.38) that, in a direct measurement, does not affect the *quantity* (3.38) that is actually measured, but affects the relation between the indication and the measurement result

EXAMPLE Amount-of-substance concentration of bilirubin in a direct measurement of haemoglobin amount-of-substance concentration in human blood plasma.

[SOURCE: ISO/IEC Guide 99:2007 2.52, modified — excludes 3 examples and 2 notes.]

3.17
international conventional calibrator
international conventional calibration material
international measurement standard
calibrator (3.6) whose *quantity* (3.38) value is not *metrologically traceable* (3.31) to the SI but is assigned by international agreement

Note 1 to entry: The *quantity* (3.38) is defined with respect to the intended clinical application.

3.18
international conventional reference measurement procedure
international conventional RMP
MP (3.27) yielding values that are not metrologically traceable to the SI but which by international agreement are used as reference values for a defined *quantity* (3.38)

Note 1 to entry: The *quantity* (3.38) is defined with respect to the intended clinical application.

3.19
international harmonisation protocol
description of a process implemented by an international body to achieve *equivalence of measured values* (3.13) within medically acceptable limits among two or more *IVD MDs* (3.21) intended for examination of the same *measurand* (3.26) for cases where there are no *higher order RMPs* (3.15) and no fit for purpose *CRMs* (3.9) or *international* conventional *calibrators* (3.17)

Note 1 to entry: A harmonisation protocol can be used to achieve standardization of measured values for a stated *measurand* (3.26) when there are no other higher order reference system components that are suitable for use.

3.20
international measurement standard
measurement standard (3.28) recognized by signatories to an international agreement and intended to serve worldwide as the basis for assigning values to other standards for the same *quantity* (3.38)

EXAMPLE 1 The international prototype of the kilogram.

EXAMPLE 2 ERM®-DA470k/IFCC for the *calibration* (3.4) of immunoassay-based in-vitro diagnostic devices or control products for the proteins certified. European Commission — Joint Research Centre (JRC), Geel, Belgium.

EXAMPLE 3 Triple point of water — the single combination of pressure and temperature at which liquid water, solid ice, and water vapour coexist in a stable equilibrium, occurring at exactly 273,16 K (0,01 °C; 32,02 °F) at a partial vapour pressure of 611,657 pascals (6,116 57 mbar; 0,006 036 59 atm).

[SOURCE: ISO/IEC Guide 99:2007 5.2, modified — Example 2 and Example 3 have been deleted. New Example 2 and Example 3 have been added]