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In vitro diagnostic medical devices —
Measurement of quantities in biological
samples — Metrological traceability
of values assigned to calibrators and
control materials

*Dispositifs médicaux de diagnostic in vitro — Mesurage des grandeurs
dans des échantillons d'origine biologique — Traçabilité métrologique
des valeurs attribuées aux agents d'étalonnage et aux matériaux
de contrôle*

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Foreword

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International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 17511 was prepared by the European Committee for Standardization (CEN) in collaboration with Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

Throughout the text of this document, read "...this European Standard..." to mean "...this International Standard...".

For the purposes of this International Standard, the CEN annex regarding fulfilment of European Council Directives has been removed.

Contents

Foreword

This document (EN ISO 17511:2003) has been prepared by Technical Committee CEN/TC 140 "In vitro diagnostic medical devices", the secretariat of which is held by DIN, in collaboration with Technical Committee ISO/TC 212 "Clinical laboratory testing and in vitro diagnostic test systems".

This European Standard EN ISO 17511:2003 including the Amendment shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by February 2004, and conflicting national standards shall be withdrawn at the latest by February 2004.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the European Confederation of Laboratory Medicine (ECLM), and the European Diagnostic Manufacturers Association (EDMA) have contributed to its preparation.

This standard includes a Bibliography.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland and the United Kingdom.

Introduction

For measurements of quantities in laboratory medicine, it is essential that the quantity is adequately defined and that the results reported to the physicians or other health care personel and patients are adequately accurate (true and precise) to allow correct medical interpretation and comparability over time and space.

NOTE   In this European Standard the concept "accuracy of measurement" (see 3.1) is related to both "trueness of measurement" (see 3.33) and "precision of measurement" (see 3.23) whereas the Directive 98/79/EC on in vitro diagnostic medical devices uses the term "accuracy" instead of "trueness".

To allow 'correct medical interpretation' involves more than the metrological (analytical) aspects of the traceability chain. As the measurement results are eventually used by the physician for the benefit of the patients, the physician should gather information on a number of other aspects, such as knowledge about the pre- and post-analytical phase, the diagnostic sensitivity and specificity, and relevant reference interval(s). The present European Standard deals only with the analytical aspects of measurements in Laboratory Medicine (see also 1 e)).

The measurement of quantities in biological samples requires reference measurement systems including:

- the definition of the analyte in the biological sample with regard to the intended clinical use of the measurement results;

- a reference measurement procedure for the selected quantity in human samples;

- suitable reference materials for the selected quantity, e.g. primary calibrators and secondary matrix-based calibrators that are commutable.

The trueness of measurement of a value assigned to a defined quantity of a calibrator or trueness control material, depends on the metrological traceability of the value through an unbroken chain of alternating measurement procedures and measurement standards (calibrators), usually having successively decreasing uncertainties of measurement (see Figure 1). The uncertainty of the value assigned to a given calibrator or trueness control material depends on the stated metrological traceability chain and the combined uncertainties of its links.

The ideal end-point of a metrological traceability chain is the definition of the relevant unit of the International System of Units (SI), but the selection of steps and the level at which metrological traceability for a given value stops, depend on the availability of higher order measurement procedures and calibrators. In many cases, at present, there is no metrological traceability above the manufacturer's selected measurement procedure or the manufacturer's working calibrator. In such cases, trueness is referred to that level of the calibration hierarchy until an internationally agreed reference measurement procedure and/or calibrator becomes available.

The objective of a chosen metrologically traceable calibration is to transfer the degree of trueness of a reference material, and/or reference measurement procedure, to a procedure that is of a lower metrological order, e.g. a routine procedure. Metrological traceability of calibration requires that the reference and routine measurement procedures measure the same measurable quantity with an analyte of the same pertinent characteristics.

In this context, it is important to recognize that different procedures purporting to measure the same quantity may in fact give different results when applied to a particular sample or reference material. This may arise, for example, when two or more immunoprocedures purporting to measure the concentration of a hormone such as thyrotropin (thyroid stimulating hormone, TSH) are applied to a reference material of the hormone, because the respective reagents recognize and react to different extents with various epitopes in the material, thus leading to results for different although related quantities.

Laboratory medicine routinely provides results for 400 to 700 types of quantity. For most of these, the metrological traceability of the assigned value for a product calibrator stops after only one metrologically higher step consisting of a (reference) measurement procedure, or after two steps consisting of a measurement procedure and a (reference) calibrator. The reason is that many of such quantities are related to mixtures of molecular species with clinically relevant properties in common, but with different structures and molecular masses in varying proportions, e.g. glycoproteins.

Depending on the possibility of metrological traceability to SI and on the availability of various metrological levels of measurement procedures and calibrators, the following five typical upper ends of the metrological traceability chain can be identified.

a) Quantities for which results of measurements are metrologically traceable to SI.

A primary reference measurement procedure and one or more (certified) primary reference materials (used as calibrators) are available. These levels exist for approximately 25 to 30 types of quantity having well defined components, e.g. some electrolytes, metabolites, steroid hormones, and some thyroid hormones. These types of quantity cover a large proportion of the routine results provided by medical laboratories (see 4.2.2, 5.2, Figures 1 and 2).

b) Quantities for which results of measurements are not metrologically traceable to SI.

1) An international conventional reference measurement procedure (see 3.12) (which cannot be called a primary reference measurement procedure) and one or more international conventional calibration materials (see 3.11) with values assigned by that procedure are available. These conditions apply for quantities with components such as HbA_{1c} (see 5.3 and Figure 3).

2) An international conventional reference measurement procedure is available but no international conventional calibration materials. These conditions apply for about 30 types of quantity with components such as haemostatic factors (see 5.4 and Figure 4).

3) One or more international conventional calibration materials (used as calibrators) with a protocol for value assignment are available, but no international conventional reference measurement procedure. These conditions apply for over 300 types of quantity, e.g., for quantities referred to World Health Organization's International Standards, such as protein hormones, some antibodies, and tumour markers (see 5.5 and Figure 5).

4) Neither reference measurement procedure nor reference materials for calibration are available. The manufacturer can establish 'in-house' measurement procedure(s) and calibrator(s) to support value assignment to his product calibrator. These conditions apply for about 300 types of quantity with components such as tumour markers and antibodies (see 5.6 and Figure 6).

The principles of the respective transfer protocols (calibration hierarchies) are presented, given the provisions of the European Standards EN 12286 on presentation of reference measurement procedures and EN 12287 on the description of reference materials.

It is the aim of metrology in laboratory medicine to improve metrological traceability for results of a type of quantity from the conditions described under b2), b3), and b4) to those of b1) by providing the missing reference measurement procedures and reference materials, based on international consensus.

The special problems of metrological traceability for values of catalytic concentration of enzymes are considered in prEN ISO 18153.

1   Scope

This European Standard specifies how to assure the metrological traceability of values assigned to calibrators and control materials intended to establish or verify trueness of measurement. The calibrators and control materials are those provided by the manufacturers as part of, or to be used together with, in vitro diagnostic medical devices.

External quality assessment (survey) samples, with proven commutability, whose values have been assigned by means of internationally agreed reference measurement systems or internationally agreed conventional reference measurement systems fall within the scope of this European Standard.

This European Standard is not applicable to:

a)   control materials that do not have an assigned value and are used only for assessing the precision of a measurement procedure, either its repeatability or reproducibility (precision control materials);

b)   control materials intended for intralaboratory quality control purposes and supplied with intervals of suggested acceptable values, each interval obtained by interlaboratory consensus with respect to one specified measurement procedure, and with limiting values that are not metrologically traceable;

c)   correlation between results of two measurement procedures at the same metrological level, purporting to measure the same quantity, because such 'horizontal' correlation does not provide metrological traceability;

d)   calibration derived from correlation between the results of two measurement procedures at different metrological levels, but with quantities having analytes of different characteristics;

e)   metrological traceability of routine results to the product calibrator and their relations to any medical discrimination limit;

f)   properties involving nominal scales, i.e. where no magnitude is involved (e.g. identification of blood cells).

2   Normative references

This European Standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text, and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies (including amendments).

EN 375:2001, *Information supplied by the manufacturer with in vitro diagnostic reagents for professional use.*

International Vocabulary of Basic and General Terms in Metrology, 2nd edition, ISO, Geneva, 1993.[1)2)]

ISO Guide 35:1989, *Certification of reference materials - General and statistical principles.*

3   Terms and definitions

For the purposes of this European Standard, the following terms and definitions apply:

3.1
accuracy of measurement
closeness of the agreement between the result of a measurement and a true value of the measurand

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[1)] This monograph has been prepared simultaneously in English and French by a joint working group consisting of experts appointed by: BIPM (International Bureau of Weights and Measures), IEC (International Electrotechnical Commission), IFCC (International Federation of Clinical Chemistry and Laboratory Medicine), ISO (International Organization for Standardization), IUPAC (International Union of Pure and Applied Chemistry), IUPAP (International Union of Pure and Applied Physics), OIML (International Organization of Legal Metrology)

[2)] The abbreviation VIM:1993 is used in this standard

[VIM:1993, 3.5]

NOTE 1   Accuracy of measurement is related to both trueness of measurement and precision of measurement.

NOTE 2   Accuracy cannot be given a numerical value in terms of the measurand, only descriptions such as 'sufficient' or 'insufficient' for a stated purpose.

NOTE 3   An estimator of an inverse measure of accuracy is "deviation", defined as 'value minus a conventional true value'.

NOTE 4   ISO 3534-1, instead of "a true value" in the definition above, uses the concept "the accepted reference value", which can be a theoretical (true), assigned, consensus, or procedure-defined value.

NOTE 5   In this standard the concept "accuracy of measurement" is related to both "trueness of measurement" (see 3.33) and "precision of measurement" (see 3.23) whereas the Directive 98/79/EC on in vitro diagnostic medical devices uses the term 'accuracy' instead of 'trueness'.

3.2
analyte
component represented in the name of a measurable quantity

EXAMPLE   In the type of quantity "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 (see 3.17).

3.3
analytical specificity
ability of a measurement procedure to measure solely the measurand

3.4
bias of measurements
difference between the expectation of the results of measurement and a true value of the measurand

NOTE   An estimator is the "statistical sample bias of measurements" which is the 'average minus its reference value'.

3.5
calibration
set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards

[VIM:1993, 6.11]

NOTE   The term "standard" here refers to "measurement standard" (see 3.19), not a written standard.

3.6
calibration transfer protocol
transfer protocol
detailed description for assigning a value of a quantity to a reference material using a specified sequence of measurement procedures calibrated by higher-order reference materials for the same type of quantity

3.7
calibrator
calibration material
reference material whose value is used for the independent variable in a calibration function

3.8
certified reference material
CRM
reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes metrological traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence

[slightly adapted from VIM:1993, 6.14]

3.9
commutability of a material
closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material, and the mathematical relationship obtained for the quantity in routine samples

3.10
influence quantity
quantity that is not the measurand but that affects the result of the measurement

[VIM:1993, 2.7]

3.11
international conventional calibrator
international conventional calibration material
calibrator whose value of a quantity is not metrologically traceable to the SI but is assigned by international agreement

NOTE   The quantity is defined with respect to the intended clinical application.

3.12
international conventional reference measurement procedure
measurement procedure yielding values that are not metrologically traceable to the SI but which by international agreement are used as reference values for a defined quantity

NOTE   The quantity is defined with respect to the intended clinical application.

3.13
international measurement standard
international standard
standard recognized by an international agreement to serve internationally as the basis for assigning values to other standards of the quantity concerned

[VIM:1993, 6.2]

3.14
matrix of a material system
matrix
totality of components of a material system except the analyte

[EN 12287:1999, 3.3]

3.15
matrix effect
influence of a property of the sample, other than the measurand, on the measurement of the measurand according to a specified measurement procedure and thereby on its measured value

NOTE 1   A specified cause of a matrix effect is an influence quantity.

NOTE 2   The term 'matrix effect' is sometimes erroneously used for the lack of commutability due to a denatured analyte or an added non-genuine component ('surrogate analyte') meant to simulate the analyte.

3.16
measurable quantity
quantity
attribute of a phenomenon, body or substance that may be distinguished qualitatively and determined quantitatively

[VIM:1993, 1.1]

NOTE 1   Properties that are expressed on a nominal scale are not measurable quantities.

NOTE 2   "Measurable quantity" is not to be confused with "analyte", see 3.2.

3.17
measurand
particular quantity subject to measurement

[VIM:1993, 2.6]

NOTE   See 3.2, Example.

3.18
measurement procedure
set of operations, described specifically, used in the performance of particular measurements according to a given method

[VIM:1993, 2.5]

3.19
measurement standard
material measure, measuring instrument, reference material or measuring system intended to define, realize, conserve or reproduce a unit or one or more values of a quantity to serve as a reference

[VIM:1993, 6.1]

NOTE 1   A given measurement standard with an assigned value for one quantity can sometimes serve as a reference material for measurement procedures yielding values for more than one type of quantity. (For example, a reference material for cholesterol also serving for cholesterol esters that are measured after hydrolysis as cholesterol).

NOTE 2   The term 'standard' is used with two meanings: "measurement standard" and "written standard". The full terms should be used when doubt can arise.

3.20
method of measurement
logical sequence of operations, described generically, used in the performance of measurements

[VIM:1993, 2.4]

NOTE   A method of measurement, due to its generalized description, does not have numerically specified performance characteristics. A given method can be the basis of one or more measurement procedures, each with inherent numerical values for its performance characteristics.

3.21
metrological traceability
property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties

[VIM:1993, 6.10]

NOTE 1   Each comparison is effected by a (reference) measurement procedure defined in a calibration transfer protocol.

NOTE 2   There are several types of traceability. Therefore the term 'metrological traceability' is used in the present text.

3.22
metrology
science of measurement

NOTE   Metrology includes all aspects both theoretical and practical with reference to measurements, whatever their uncertainty, and in whatever fields of science or technology they occur.

[VIM:1993, 2.2]

3.23
precision of measurement
closeness of agreement between independent results of measurements obtained under stipulated conditions

[ISO 3534-1:1993, 3.14]

NOTE 1   Precision of measurement cannot be given a numerical value in terms of the measurand, only descriptions such as 'sufficient' or 'insufficient' for a stated purpose.

NOTE 2   The degree of precision is usually expressed numerically by the statistical measures of imprecision of measurements, such as standard deviation and coefficient of variation, that are inversely related to precision.

NOTE 3   "Precision" of a given measurement procedure is subdivided according to the specified precision conditions. "Repeatability" relates to essentially unchanged conditions and is often termed "withinserial" or "within-run precision". "Reproducibility" relates to changes in conditions, e.g. time, different laboratories, operators, and measuring systems (including different calibrations and reagent batches).

3.24
primary reference material
reference material having the highest metrological qualities and whose value is determined by means of a primary reference measurement procedure

NOTE 1   The concept "primary calibrator" is subordinate to "calibrator" (see 3.7) and to "primary reference material".

NOTE 2   See 3.26, Note.

3.25
primary reference measurement procedure
reference measurement procedure having the highest metrological qualities, whose operation can be completely described and understood, for which a complete uncertainty statement can be written down in terms of SI units, and where results are, therefore, accepted without reference to a measurement standard of the quantity being measured

NOTE   The Consultative Committee on Amount of Substance (CCQM) uses the term "primary method of measurement", but the term "primary reference measurement procedure" in the present context is in conformity with VIM (see 3.19 with Note). The term "definitive method'" was omitted in VIM, but is sometimes used for a thoroughly investigated and evaluated reference measurement procedure (see 3.29) of high accuracy.

3.26
primary measurement standard
primary standard
standard that is designated or widely acknowledged as having the highest metrological qualities and whose value is accepted without reference to other standards of the same quantity

[VIM:1993, 6.4]

NOTE   For reference materials, the value can be obtained by applying a primary reference measurement procedure.

3.27
product calibrator
calibrator intended for use with the manufacturer's final product

3.28
reference material
RM
material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement procedure, or for assigning values to materials

NOTE 1   Adapted from VIM:1993, 6.13.

NOTE 2   The adjective 'homogeneous' refers to the physical homogeneity between macroscopic parts of the material, not to any microheterogeneity between molecules of the analyte.

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3.29
reference measurement procedure
thoroughly investigated measurement procedure shown to yield values having an uncertainty of measurement commensurate with its intended use, especially in assessing the trueness of other measurement procedures for the same quantity and in characterizing reference materials

[EN 12286:1998, 3.7]

3.30
secondary measurement standard
secondary standard
standard whose value is assigned by comparison with a primary standard of the same quantity

[VIM:1993, 6.5]

3.31
true value of a quantity
true value
value consistent with the definition of a given particular quantity

[VIM:1993, 1.19]

NOTE 1   This is a value that would be obtained by a perfect measurement.

NOTE 2   True values are by nature indeterminate.

NOTE 3   The indefinite article "a", rather than the definite article "the", is used in conjunction with "true value" because there may be many values consistent with the definition of a given particular quantity.

NOTE 4   The 'definition of a given particular quantity' may have to include the measurement procedure applied. Therefore, a true value may depend on a specified measurement procedure.

3.32
trueness control material
reference material that is used to assess the bias of measurement of a measuring system

3.33
trueness of measurement
closeness of agreement between the average value obtained from a large series of results of measurements and a true value

NOTE 1   Definition adapted from ISO 3534-1:1993, 3.12 that has '...test results and an accepted reference value' , which can be a theoretical (true), assigned, consensus, or procedure-defined value.

NOTE 2   Concerning the phrase 'a true value', see 3.31, Note 2.

NOTE 3   Trueness of measurement cannot be given a numerical value in terms of the measurand, only ordinal values (e.g. sufficient, insufficient).

NOTE 4   The degree of trueness is usually expressed numerically by the statistical measure bias that is inversely related to trueness and is the difference between the expectation of the results of measurement and a true value of the measurand.

3.34
uncertainty of measurement
parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand

[VIM:1993, 3.9]

NOTE 1   The parameter can be, for example, a standard deviation (or a given multiple of it), or the half-width of an interval having a stated level of confidence.

NOTE 2   The components of uncertainty are evaluated experimentally from statistical distributions (Type A) or evaluated from assumed probability distributions based on experience or other information (Type B) (see [10]). All components are expressed as standard uncertainties that are combined into one final expression.

3.35
validation
confirmation, through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled

[EN ISO 9000:2000, 3.8.5]

3.36
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

[EN ISO 9000:2000, 3.8.4]

3.37
working measurement standard
working standard
standard that is used routinely to calibrate or check material measures, measuring instruments or reference materials

[VIM:1993, 6.7]

4   Metrological traceability chain and calibration hierarchy

4.1 Principles

4.1.1   Before a metrological traceability chain is established, the measurable quantity (measurand) shall be defined with reference to the intended use of the result in medical decisions. The details of this definition shall comprise as appropriate:

a)   intended use of the quantity with regard to a particular medical decision (e.g. choriogonadotropin (hCG) in plasma as a tumour marker or for the detection and monitoring of pregnancy);

b)   biological system (e.g. human serum) and any pertinent component (e.g. sodium ion) to be characterized by the quantity as defined by relevant international scientific organizations (e.g. IFCC, ICSH), and/or the manufacturer;

c)   kind-of-quantity (e.g. amount-of-substance concentration) defined by the General Conference on Weights and Measures (CGPM), ISO, WHO, international scientific organizations, and/or the manufacturer;

d)   unit of measurement (e.g. mmol/l), if any, defined by CGPM, WHO, international scientific organizations, and/or the manufacturer.

4.1.2   The objective of metrological traceability shall be to enable the results obtained by the calibrated routine procedure to be expressed in terms of the values obtained at the highest available level of the calibration hierarchy. The metrological traceability chain shall be established before initiating the final measurement, and shall be described by a calibration hierarchy descending in the opposite direction, that is from the metrologically highest reference to the result of the end-user (see Figure 1).

4.1.3   Each level in the calibration hierarchy shall be a measurement procedure or a measurement standard, the latter being a measuring system or a reference material functioning as a calibrator.

4.1.4   A given measurement standard with its assigned value shall serve to calibrate the measurement standard at the next lower level by way of a measurement procedure as specified in a transfer protocol.

NOTE   When the calibration function is based on more than one calibrator, such calibrators can be separate in origin or be produced from one measurement standard, e.g. by dilution.

4.1.5   The value assigned to a measurement standard at a given level shall be associated with an uncertainty of measurement that shall include inherited consecutive uncertainty contributions from measurement standards and measurement procedures at all higher levels of the calibration hierarchy.

NOTE   The chosen measure of uncertainty preferably should be estimated according to the GUM (see clause 6).

4.1.6   To ensure the validity of a metrological traceability chain, the quantity shall be the same at all levels. The analytical specificities of the described routine procedure and metrologically higher reference measurement procedures as well as the stability and commutability of the calibrators shall be known or investigated. The outcome shall be described in the manufacturer's technical documentation.

4.1.7   The responsibility of the manufacturer for describing the metrological traceability chain shall start at the value of the manufacturer's product calibrator and end at the metrologically highest reference used by the manufacturer. The uncertainty of this reference shall include any further upwards contributions to uncertainty.

4.2 Structure and nomenclature

4.2.1   As the structure of an actual metrological traceability chain depends on the metrological possibilities, any description of the elements of the chain shall include or refer to definitions of terms and statements of the metrological properties of measuring systems and reference materials involved.

NOTE 1   The series of measurement standards defined in VIM is based on the needs of calibration hierarchies for quantities in physics, such as a length, a time, a temperature, a pressure, an electrical potential difference (voltage), a volume, and an absorbance, and comprises

- primary measurement standard,

- secondary measurement standard,

- reference measurement standard,

- working measurement standard.

NOTE 2   For practical purposes - especially for quantities in chemistry - there should be a distinction between the elements in the calibration hierarchy that are measuring systems, described in and operated according to a measurement procedure, and those that are used for calibration of the measuring systems. The latter type is called calibration material or calibrator. In chemical measurement the concept "reference material" includes "calibration material" and "trueness control material".

4.2.2   In a given calibration hierarchy providing metrological traceability to SI, the following concepts shall be identified as appropriate (see Figure 1), see also 4.2.3 and 4.2.4.

a) *SI unit of measurement*, whether base or derived, to which metrological traceability preferably shall refer, for example mole, kilogram, mole per cubic metre (= millimole per litre), gram per kilogram (= 10^{-3}).

b) *Primary reference measurement procedure* shall be based on a principle of measurement proved to be analytically specific, providing metrological traceability to an SI unit of measurement without reference to a calibrator for the same quantity, and having a low uncertainty of measurement.

NOTE 1   The International Committee on Weights and Measures (CIPM) in 1994 formed a Consultative Committee on Amount of Substance (CCQM), which provisionally identified the following potential principles of measurement for primary reference measurement procedures: isotope dilution-mass spectrometry, coulometry, gravimetry, titrimetry, freezing-point depression measuremet for osmolality determination.

NOTE 2   A primary reference measurement procedure is usually endorsed by an international or national metrology institute or by an international scientific body. National primary reference measurement procedures should not be developed. The measurements preferably should be performed by a metrology institute or a laboratory accredited by a recognized accrediting body as a calibration laboratory for that measurement procedure.

NOTE 3   More than one primary reference measurement procedure can exist at a given time for assigning values of quantities of a given kind to primary calibrators. (The values obtained by two such procedures for a given measurand should not be significantly different within a stated uncertainty at a certain level of confidence).

c) *Primary calibrator* that is an embodiment of the unit of measurement with the smallest achievable uncertainty of measurement. The primary calibrator shall have its value assigned either directly by a primary reference

measurement procedure or indirectly by determining the impurities of the material by appropriate analytical methods. The material usually is highly purified containing a physico-chemically well-defined analyte, examined for stability, compositional integrity, and accompanied by a certificate (certified reference material, CRM).

NOTE 4   The certification of a primary calibrator usually occurs in laboratories having the highest metrological expertise, such as an international or national metrology institute.

d)   *Secondary reference measurement procedure* shall describe a measuring system which is calibrated by one or more primary calibrators.

NOTE 5   A secondary reference measurement procedure can be established in national metrology institutes or in reference measurement laboratories accredited for that measurement procedure by a recognized accrediting body.

NOTE 6   A secondary reference measurement procedure can be based on a principle of measurement different from that of a primary procedure.

e)   *Secondary calibrator* shall have its value assigned according to one or more secondary reference measurement procedures and is usually accompanied by a certificate.

NOTE 7   A secondary calibrator usually disseminates a unit of measurement from a national metrology institute to accredited calibration laboratories and the manufacturer's calibration centre.

NOTE 8   A secondary calibrator can be, e.g., a material with a matrix resembling those of the samples of human origin to be measured by the end-users' routine measurement procedures.

f)   *Manufacturer's selected measurement procedure* shall define a measuring system which is calibrated by one or more primary or secondary calibrators when available.

NOTE 9   A manufacturer's selected measurement procedure can be a secondary reference measurement procedure (see 4.2.2.d)).

g)   *Manufacturer's working calibrator* shall have its value assigned according to one or more of the manufacturer's selected measurement procedures. This calibrator is sometimes called "manufacturer's master calibrator" (or "in-house calibrator"). The calibration material shall have demonstrated commutability as regards the manufacturer's selected measurement procedure and the procedure to be calibrated.

NOTE 10   A manufacturer's working calibrator can be, e.g., a material with a matrix resembling those of the samples of human origin to be measured by the end-users' routine measurement procedures.

h)   *Manufacturer's standing measurement procedure* shall define a measurement procedure prescribing calibration by one or more of the manufacturer's working calibrators or higher types of calibrator and is validated for analytical specificity.

NOTE 11   The manufacturer's standing measurement procedure can be based on the same principle and method of measurement as the routine measurement procedure, but should have a lower uncertainty of measurement obtained through, e.g., a larger number of replicates and a stricter control system.

i)   *Manufacturer's product calibrator* shall have its value assigned according to the manufacturer's standing measurement procedure and is intended for calibration of the end-user's routine measurement procedure.

NOTE 12   A manufacturer's product calibrator can be, e.g., a material with a matrix resembling those of the samples of human origin to be measured by the end-users' routine measurement procedures.

j)   *End-user's routine measurement procedure* shall describe a measuring system, often supplied by a manufacturer, calibrated by one or more manufacturer's product calibrators.
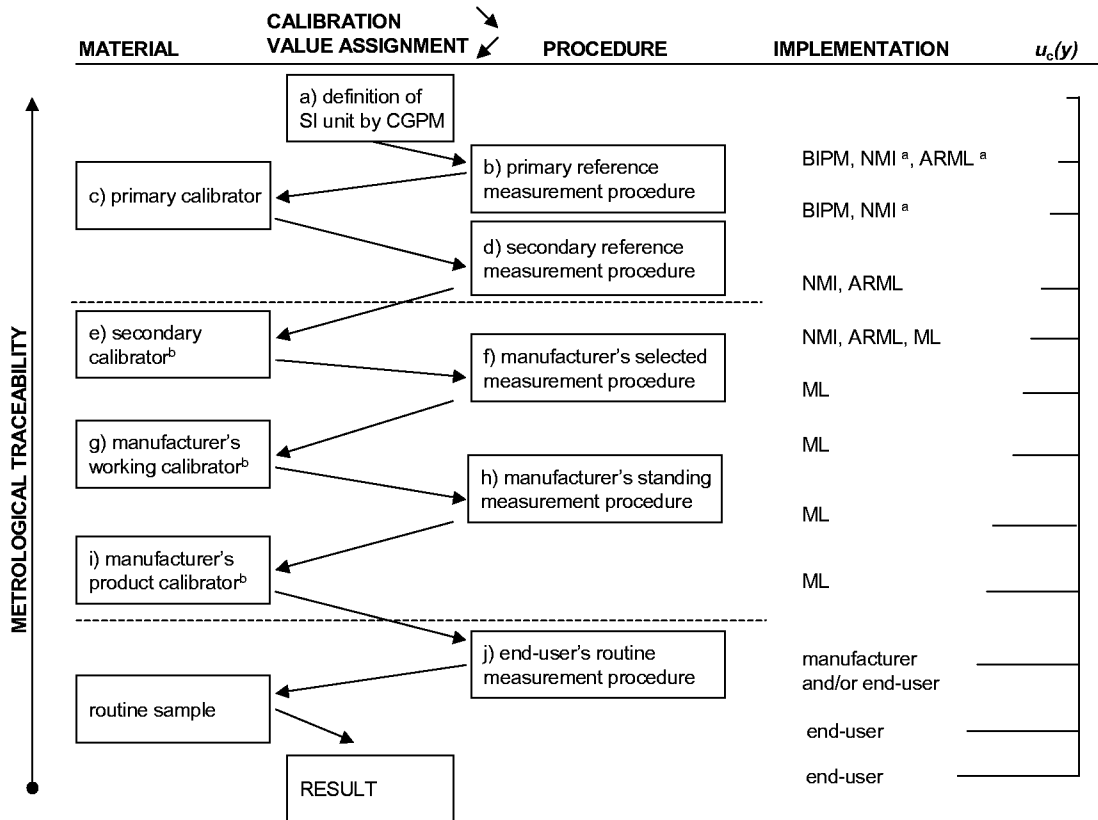
Abbreviations: ARML Accredited reference measurement laboratory (such a laboratory may be an independent or a manufacturer's laboratory); BIPM International Bureau of Weights and Measures; CGPM General Conference on Weights and Measures; ML Manufacturer's laboratory; NMI National metrology institute.

The symbol $u_c(y)$ stands for combined standard uncertainty of measurement.

The horizontal bars at the extreme right under $u_c(y)$ are not to scale.

Details of concepts are given in 4.2.2 according to lettering a) to j).

The responsibility of the manufacturer for metrological traceability shall begin at the assigned value for a product calibrator and end at the secondary calibrator or secondary reference measurement procedure as the case may be and if such exist. (The former segment is delimited by two horizontal broken lines). The manufacturer, however, shall also be responsible for the Instructions for use.

Metrological traceability of a value assigned to a trueness control material shall utilize the calibration hierarchy shown as appropriate, substituting in i) with 'manufacturer's product trueness control material'.

Figure 1 - Extensive calibration hierarchy and metrological traceability to SI
(see 4.2.2) *(to be continued)*

NOTE 1   Depending upon availability of measurement procedures and calibrators, a metrological traceability chain can stop at any level from the end-user's routine measurement procedure (j)) upwards.

NOTE 2   When no primary or secondary calibrator is available, the calibrator of the highest metrological quality should preferably be an international conventional calibrator.

NOTE 3   When no primary or secondary reference measurement procedure exists, the highest placed procedure should preferably be an international conventional reference measurement procedure.

NOTE 4   The extensive calibration hierarchy shown can be shortened as appropriate, but still provide metrological

traceability to an SI unit, by omitting an even number of consecutive levels, except for a), b) and i).

a With endorsement by international scientific/medical organizations, e.g. IFCC and WHO.

b The calibrator can be a material with a matrix resembling those of the samples of human origin to be measured by the end-user's routine measurement procedure.

Figure 1 - Extensive calibration hierarchy and metrological traceability to SI
(see 4.2.2) *(end)*

4.2.3   Where pairs of consecutive levels (calibrator and procedure or vice versa) of a calibration hierarchy are omitted, uncertainty shall be reduced. In principle, the elements of 4.2.2 a), b), i) shall be considered indispensable if metrological traceability to SI is to be claimed for the value assigned to a manufacturer's product calibrator.

4.2.4   When the upper levels of the calibration hierarchy described in 4.2.2 do not exist, the metrologically highest placed measurement procedure or calibration material referred to shall be stated (see 5.3 to 5.6). In some cases, this is the manufacturer's working calibrator (see 4.2.2 g)) or the manufacturer's standing measurement procedure (see 4.2.2. h)).

4.2.5   Apart from the terms for calibrators given in 4.2.2.c), e), g), and i), a given calibrator shall be further characterized, as appropriate, by elements from any of the following types of information:

a)   recognition (e.g. international, regional, national),

b)   issuing authority (e.g. WHO, BCR, IRMM, NIST)[3]

c)   certificate (certified, non-certified),

d)   origin (e.g. inorganic, human or animal, vegetable, or microbial),

e)   production (e.g. synthetic, natural, recombinant),

f)   molecular form(s) of or surrogate for the analyte (e.g. steric isomer for an amino acid, or glycerol for glycerol ester),

g)   matrix (e.g. buffered bovine albumin solution),

h)   state(s) of aggregation (gas, liquid, solid),

i)   phase(s) (solution, suspension, lyophilized),

j)   intended use.

4.2.6   For a measurable quantity having values not metrologically traceable to SI, no primary reference measurement procedure or primary calibrator shall exist. When available, the highest level procedure or calibrator shall be an international conventional reference measurement procedure (see 3.12) or an international conventional calibration material (see 3.11) endorsed by an international metrological body or an international scientific organization. Implementation shall be by metrology institutes or accredited reference measurement laboratories providing metrological traceability to an international level if available.

NOTE 1   Various transfer protocols are given in 5.3 to 5.5.

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[3] WHO World Health Organization, BCR Community Bureau of Reference (European Union), IRMM Institute of Reference Materials and Measurements (European Union), NIST National Institute of Standards and Technology (USA)

NOTE 2   International agreement on such reference measurement systems without metrological traceability to SI is necessary to avoid that different national or regional reference measurement systems provide different metrological traceability chains giving different results on patient samples, thus hindering comparability over time and space.

NOTE 3   The WHO Expert Committee on Biological Standardization (ECBS) establishes international biological reference materials called "International Standards (IS)" (and previously "International Reference Preparations (IRP)") for use with bioprocedures and immunoprocedures (see Annex A, WHO). For the first batch of such a material, an "international unit" is defined as an arbitrarily specified amount of the material and characterized by its specified biological activity. Subsequent batches are calibrated by interlaboratory collaborative measurements against the previous material. The batches in a series are specified by "1st IS", "2nd IS", etc. The assigned value of such a reference material, even when it is highly purified, is related to a dedicated biological measurement procedure without metrological traceability to SI units. Such a material, therefore, cannot be called a primary reference material (see 3.24).

NOTE 4   An international conventional calibration material (e.g. WHO International Standard) can only be used as calibrator if the material has been developed on the basis of a clear definition of the quantity related to the intended clinical application and if the assigned value of the material has an uncertainty which is acceptable for the calibration of routine measuring systems. Some WHO International Standards were originally intended to serve as calibrators for in vivo measurement procedures based on a biological activity (especially for therapeutic purposes). The use of such materials to calibrate in vitro immunoprocedures may present several problems (see 4.3).

NOTE 5   A measurement procedure giving results not metrologically traceable to SI can still require equipment for which such traceability is needed, e.g. involving volume, time, mass, and pressure.

4.3 Considerations in establishing metrological traceability

4.3.1   The following pitfalls in establishing metrological traceability shall be considered.

a)   Insufficient definition of the analyte in the human samples.

b)   Technical problems due to a realization of the unit of amount-of-substance, the mole, as an ultrapure material of a given chemical compound (see also 4.2.6, NOTE 2).

c)   Heterogeneity of the analyte in the calibrator (isoforms, derivatives) making physico-chemical description difficult, e.g. in case of enzymes, antibodies, and glycoproteins.

d)   Measurement procedures having different specificities and selectivities towards the analyte in a given calibrator.

NOTE 1   This problem concerns the series of measurement procedures in a given calibration hierarchy, including the routine procedure, as well as a set of two or more routine procedures using the same manufacturer's product calibrator, and can invalidate the commutability of the calibrator.

NOTE 2   This problem is typically met in immunoprocedures, where antibodies used in different procedures can have different reactivity towards the epitope(s) of the analyte antigen *or* the antigens used as reagents can have different reactivity towards the analyte antibody.

e)   The human samples to be measured having analytes with individually different microheterogeneity from that of the calibrator, e.g., in the case of measurement of (total) protein concentration in serum by biuret reaction calibrated by an albumin solution; immunochemical measurement of ferritin concentration in sera with various analyte microheterogeneity where individual isoforms are recognized to different degrees by different monoclonal antibodies.

f)   Human samples having matrices different from that of the calibrator.

g)   Calibrators with an inappropriate "surrogate analyte".

h)   Physical or chemical modification during measurement of sample including analyte according to ISO Guide 35:1989, 9.3.1, e.g. by denaturation.

4.3.2   When a set of native human samples is used as secondary calibrators (see 4.2.2.e)) [or alternatively as manufacturer's working calibrators (see 4.2.2.g))] to ensure commutability at that level through relevant compositions of analyte and matrix, then this set of samples shall span the measuring interval to the extent practical.

NOTE 1   If the analyte of a sample has to be augmented or depleted, the commutability of the modified sample should be validated.

To each sample a value and uncertainty shall be assigned by a measurement procedure of a higher level. The set of human samples shall be used to calibrate the manufacturer's selected measurement procedure (see 4.2.2.f)) [or the manufacturer's standing measurement procedure (see 4.2.2.h))] which is then used to assign value(s) to the manufacturer's working calibrator(s) (see 4.2.2.g)) [or the manufacturer's product calibrator(s) (see 4.2.2.i))].

When a set of human samples functions as a secondary calibrator (4.2.2.e)) to calibrate the manufacturer's selected measurement procedure (4.2.2.f)), the manufacturer's working calibrator (4.2.2.g)), to ensure metrological traceability, shall be measured in addition by the chosen higher-level measurement procedure (e.g. by the measurement procedure used for assigning values to the set of human samples). The values obtained by these measurements shall be included in the product-related technical documentation.

NOTE 2   The results of these measurements should facilitate the evaluation of the analytical specificity of the manufacturer's selected measurement procedure, and enable assessment of the commutability of the working calibrator.

NOTE 3   The manufacturer's working calibrator (4.2.2.g)) can be a designated representative batch of the product calibrator [or trueness control material]. In this case, only the single designated working calibrator batch requires direct measurement of the measurand with the chosen higher-level measurement procedure.

When a set of human samples functions as a working calibrator (4.2.2.g)) to calibrate the manufacturer's standing measurement procedure (4.2.2.2.g)), the product calibrator (4.2.2.i)) [or trueness control material], to ensure metrological traceability, shall be measured in addition by the chosen higher-level measurement procedure (e.g. by the measurement procedure used for assigning values to the set of human samples). The values obtained by these measurements shall be included in the product-related technical documentation.

NOTE 4   When batches of product calibrator [or trueness control material] are manufactured successively following a stable formulation and manufacturing process, and batch to batch homogeneity and stability is demonstrated, direct measurement of the values of the measurand in the product calibrator [or trueness control material] with the chosen higher-level measurement procedure need occur with one representative batch only. For any subsequent batches of product calibrator [or trueness control material], the value of the measurand, as determined with the higher-level measurement procedure, can be estimated based on prior experience. Metrological traceability to higher order calibrators and procedures claimed for the representative product calibrator [or trueness control material] batch is applicable as well to any successive batch.

The validation of the commutability of the pertinent calibrators (see 7.2) and of the metrological traceability of their assigned values (see 7.3 to 7.7) shall not use the same set of native human samples.

4.4 Functions of reference materials

4.4.1   Calibrators (see 3.7) shall have an assigned value with a known uncertainty of measurement and shall have the purpose of calibrating a measuring system, thereby establishing metrological traceability of a measurement result obtained by that system.

4.4.2   Trueness control materials (see 3.32) intended to assess bias of measurement shall have an assigned value metrologically traceable to a measurement procedure or calibration material of higher metrological order. The value shall have a known uncertainty of measurement which shall not exceed that of the product calibrator.

4.4.3   A given reference material shall only be used as either a calibrator or a control material in a given measuring system.

5   Calibration transfer protocols

5.1 Availability and structure

A calibration transfer protocol shall be formulated for the assignment, by available reference materials and reference measurement procedures, of metrologically higher order to a given reference material of a value related to a given quantity. The description of a calibration transfer protocol shall include as relevant:

a)   rationale for selection of reference materials, and their stability and commutability;

b)   rationale for selection of measurement procedures including equipment;

c)   appropriate statistical methods;

d)   evaluation of matrix effects and any modifications of the analyte.

NOTE 1   One of the problems encountered by both manufacturers and users of in vitro diagnostic medical devices is the limited availability of reference materials, certified or not, showing, in a given measuring system, a behaviour of analyte and matrix similar to that of the corresponding analyte and matrix present in the routine human samples (blood, plasma, serum, urine, etc.) (see 4.3). Also, reference measurement procedures do not exist for many measurands.

NOTE 2   Where available reference materials at a given level of the calibration hierarchy can be lacking in commutability, use of a set of human samples spanning the whole of the measuring interval is permissible (see 4.3.2).

NOTE 3   The final choice of metrological levels in a given case depends on the acceptable uncertainty of measurement of the end result, availability of procedures and calibrators, technology, and economics. These factors create a dynamic background with a trend towards international recognition and metrological traceability to SI.

NOTE 4   Typical examples of calibration transfer protocols with calibration hierarchies selected from the complete series of measurement procedures and calibrators listed and generally described in 4.2.2 and Figure 1 are given in 5.2 to 5.6 and related Figures 2 to 6.

5.2 Cases with primary reference measurement procedure and primary calibrator(s) giving metrological traceability to SI

The calibration hierarchy shall, in principle, be the following (see Figure 2), which applies to measurable quantities with analytes such as electrolytes, metabolites, glucose, cholesterol, steroid hormones and some thyroid hormones, and drugs:

- *Primary reference measurement procedure* (see 4.2.2.b))

EXAMPLE 1   For cortisol in blood plasma, gravimetry combined with assessment of impurities by chemical methods.

- *Primary calibrator* (see 4.2.2.c))

EXAMPLE 2   Cholesterol as SRM 911b from the National Institute of Standards and Technology (NIST, Gaithersburg, MD, US); mass fraction 0,998 ± 0,001 where 'the purity and estimated uncertainty is based upon scientific judgement and evaluation of numerous analytical tests applied to this SRM in the certification process. The uncertainty given approximates two standard deviations about the certified value'. (Thus the value 0,001 is the expanded uncertainty with a coverage factor $k = 2$, giving a level of confidence of approximately 0,95.)

- *Secondary reference measurement procedure* (see 4.2.2.d))

EXAMPLE 3   For the concentration of cortisol in blood plasma, isotope dilution-gas chromatography-mass spectrometry (ID-GC/MS).

- *Manufacturer's working calibrator(s)* (see 4.2.2.g)) as defined by the manufacturer and having value(s) assigned either by

a)   gravimetry, i.e. weighing the analyte in the form of a primary calibrator and weighing the matrix; or

b)   measurement, i.e. applying a primary or secondary reference measurement procedure.

- *Manufacturer's standing measurement procedure* (see 4.2.2.h))

- *Manufacturer's product calibrator(s)* (see 4.2.2.i))
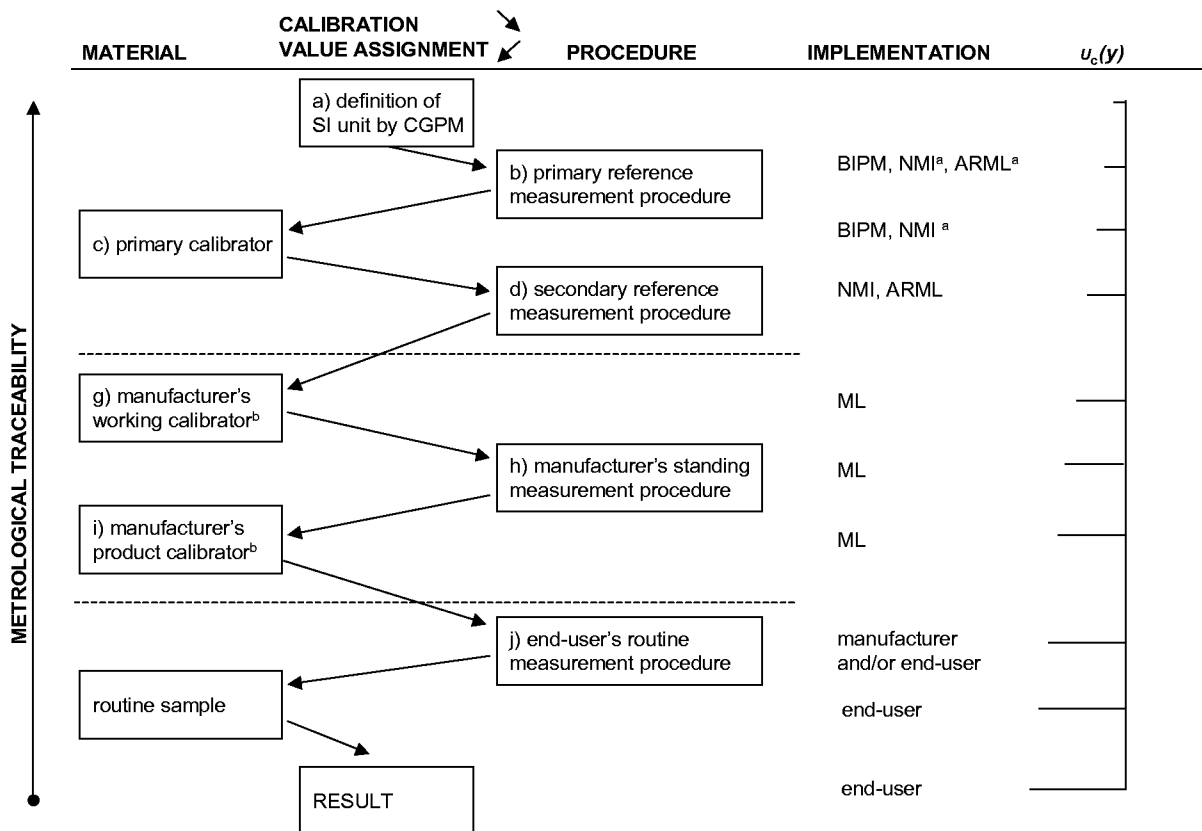
Figure 2 - Selected calibration hierarchy and metrological traceability to SI
(see 5.2 and Figure 1)

[a] With endorsement by international scientific/medical organizations, e.g. IFCC and WHO.

[b] The calibrator can be a material with a matrix resembling those of the samples of human origin to be measured by the end-user's routine measurement procedure.

5.3 Cases with international conventional reference measurement procedure (which is not primary) and international conventional calibrator(s) without metrological traceability to SI

The calibration hierarchy shall, in principle, be the following (see Figure 3), which applies to quantities involving components, such as haemoglobin $A1_c$ (in preparation):

- *International conventional reference measurement procedure* (see 4.2.6)

EXAMPLE 1   For the amount-of-substance fraction of HbA_{1c} in blood haemoglobin, a candidate high-pressure liquid chromatography-mass spectrometry(HP-LC/MS) [13]
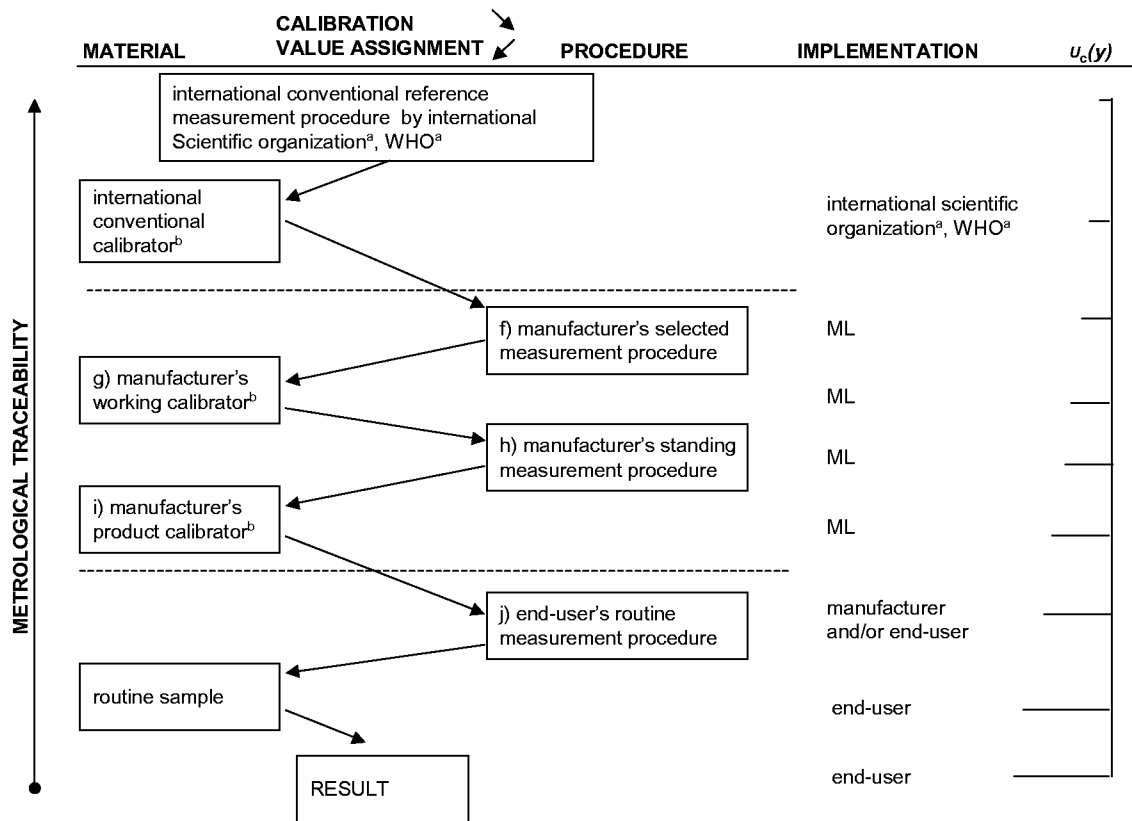
- *International conventional calibrator* (see 4.2.6)

EXAMPLE 2   For the amount-of-substance concentration of haemoglobin(Fe) in blood, absorption spectrometry of its cyanide derivative is calibrated by CRM 522 haemiglobin cyanide(HiCN) in bovine blood lysate from Community Bureau of Reference (EU-BCR) with amount-of-substance concentration (Hi(Fe)CN); (49,61 ± 0,08) μmol/l where the expanded uncertainty given is half of the interval with a level of confidence of 0,95.

- *Manufacturer's selected measurement procedure* (see 4.2.2.f))

- *Manufacturer's working calibrator*(s) (see 4.2.2.g)) as defined by the manufacturer and having value(s) assigned either by

a)   gravimetry, i.e. weighing the analyte in the form of an international calibrator and weighing the matrix; or

b)   measurement, i.e. applying the manufacturer's selected reference measurement procedure.

- *Manufacturer's standing measurement procedure* (see 4.2.2.h))

- *Manufacturer's product calibrator*(s) (see 4.2.2.i))

^aIn collaboration with BIPM, NMIs, ARMLs and with manufacturers.

^bThe calibrator can be an appropriate surrogate reference material or a human sample.

Figure 3 - Calibration hierarchy and metrological traceability to an international conventional reference measurement procedure and international conventional calibrator(s), neither of which are primary (see 5.3 and Figure 1)
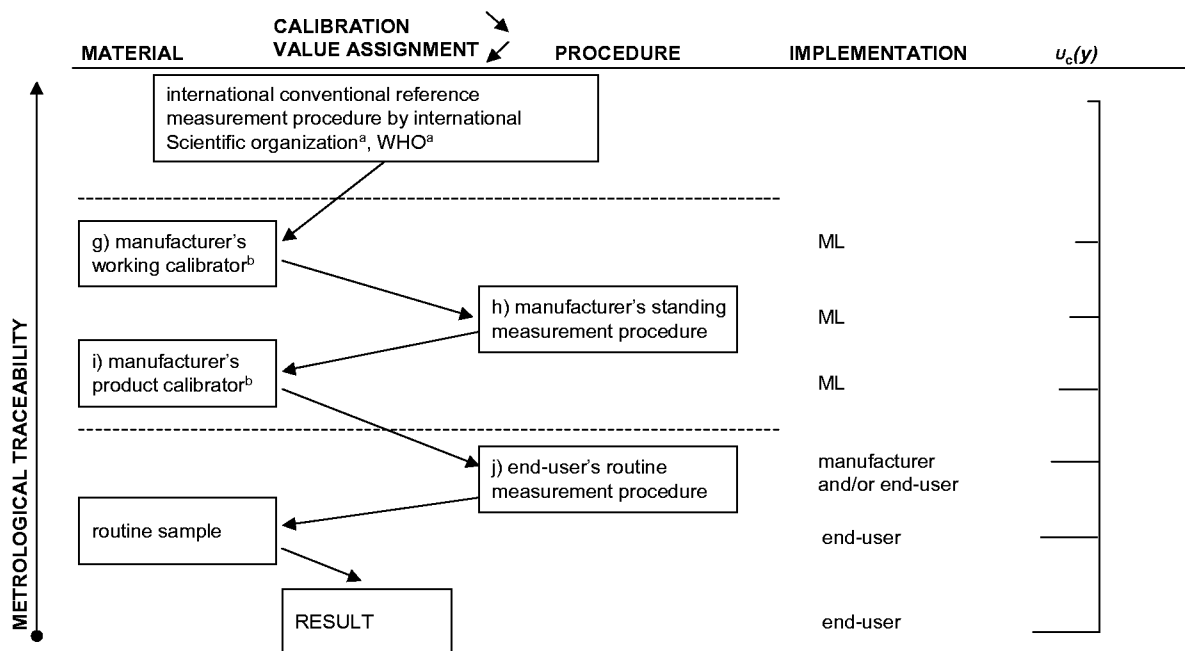
5.4 Cases with international conventional reference measurement procedure (which is not primary) but no international conventional calibrator and without metrological traceability to SI

The calibration hierarchy shall, in principle, be the following (see Figure 4), which applies to quantities involving components such as HDL-cholesterols, blood cells, and some haemostatic factors:

- *International conventional reference measurement procedure* (see 4.2.6)

EXAMPLE   Measurement procedure specified by the International Council for Standardization in Haematology (ICSH) for the measurement of the number concentration of erythrocytes and leukocytes in human blood (Clin Lab Haemat 1994;16:131-8).

- *Manufacturer's working calibrator(s)* (see 4.2.2.g)) having values assigned by the international reference measurement procedure

- *Manufacturer's standing measurement procedure* (see 4.2.2.h))

- *Manufacturer's product calibrator(s)* (see 4.2.2.i))

	CALIBRATION			
MATERIAL	VALUE ASSIGNMENT	PROCEDURE	IMPLEMENTATION	$u_c(y)$

international conventional reference measurement procedure by international Scientific organization[a], WHO[a]

g) manufacturer's working calibrator[b] — ML

h) manufacturer's standing measurement procedure — ML

i) manufacturer's product calibrator[b] — ML

j) end-user's routine measurement procedure — manufacturer and/or end-user

routine sample — end-user

RESULT — end-user

METROLOGICAL TRACEABILITY

[a] In collaboration with BIPM, NMIs, ARMLs and with manufacturers.

[b] The calibrator can be an appropriate surrogate reference material or a human sample.

Figure 4 - Calibration hierarchy and metrological traceability to an international conventional reference measurement procedure that is not primary and with no international conventional calibrator (see 5.4 and Figure 1)

5.5 Cases with international conventional calibrator (which is not primary) but no international conventional reference measurement procedure and without metrological traceability to SI

The calibration hierarchy shall, in principle, be the following (see Figure 5), which applies to quantities involving components such as hepatitis B surface antigen (subtype ad) and choriogonadotropin as well as antibodies:

- *International conventional calibrator(s)* with a value, in a defined non-SI unit if appropriate (such as WHO international unit), assigned according to an internationally accepted protocol (see 4.2.6) (Reports of the Expert Committee on Biological Standardization's yearly meetings, WHO Technical Report series 1969-1997, and WHO Weekly Epidem Rec 1997-1999).

NOTE   The assigned value should be accompanied by an uncertainty.

- *Manufacturer's selected measurement procedure* (see 4.2.2.f))

- *Manufacturer's working calibrator(s)* (see 4.2.2.g)) defined and produced as in 5.3.

- *Manufacturer's standing measurement procedure* (see 4.2.2.h))

- *Manufacturer's product calibrator(s)* (see 4.2.2.i))
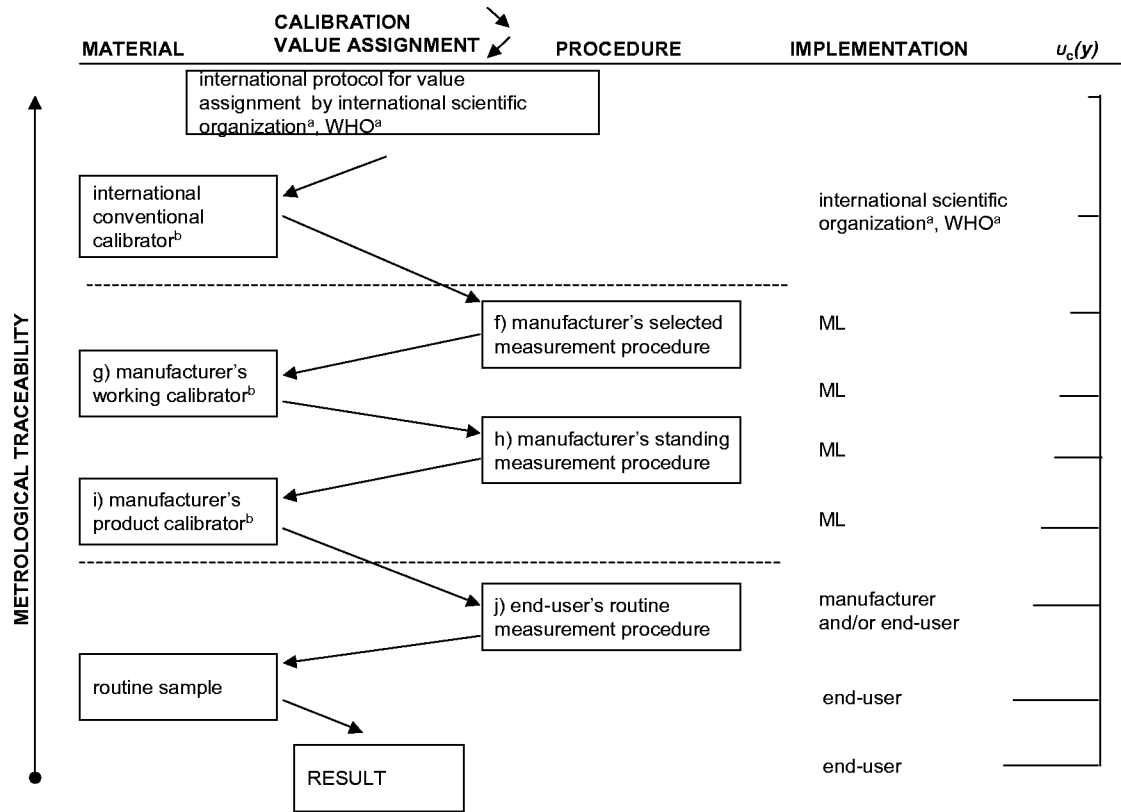
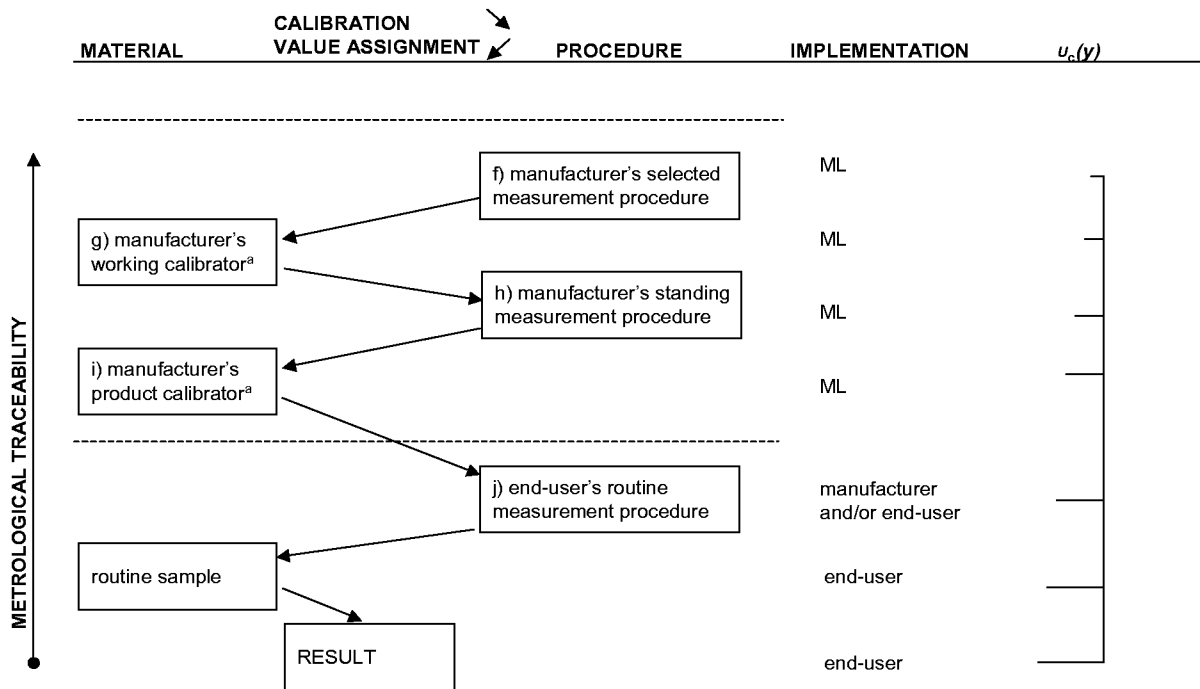[a] In collaboration with BIPM, NMIs, ARMLs and with manufacturers.

[b] The calibrator can be an appropriate surrogate reference material or a human sample.

Figure 5 - Calibration hierarchy and metrological traceability to an international conventional calibrator that is not primary and with no international conventional reference measurement procedure (see 5.5 and Figure 1)

5.6 Cases with manufacturer's selected measurement procedure but neither international conventional reference measurement procedure nor international conventional calibrator and without metrological traceability to SI

The calibration hierarchy shall, in principle, be the following (see Figure 6), which applies to quantities involving analytes such as fibrin degradation products(D-dimer), and tumour markers such as cancer antigen 125 (CA-125) as well as antibodies towards antigens such as *Chlamydia*:

- *Manufacturer's selected measurement procedure* (see 4.2.2.f))

- *Manufacturer's working calibrator(s)* (see 4.2.2.g))

- *Manufacturer's standing measurement procedure* (see 4.2.2.h)) that sometimes is identical with the selected measurement procedure

- *Manufacturer's product calibrator(s)* (see 4.2.2.i))

^a The calibrator can be an appropriate surrogate reference material or a human sample.

Figure 6 - Calibration hierarchy and metrological traceability to the manufacturer's selected measurement procedure that is not primary (see 5.6 and Figure 1)

5.7 Trueness control materials

5.7.1   Trueness control materials shall have:

a)   a matrix similar to that of the samples to be measured according to the measurement procedure under control;

NOTE 1   This is in contrast to calibrators at the metrologically higher levels, where a high purity component, often in a simple matrix, is preferred.

b)   a value with an uncertainty of measurement appropriate to the intended use.

NOTE 2   In principle, transfer protocols for assigning target values to trueness control materials intended for verifying trueness of measurement resemble the protocols used for calibrators.

5.7.2   Depending on their intended use, trueness control materials shall be assigned a value either at the same or at a higher level than the respective product calibrator(s) in a given calibration hierarchy.

6   Expression of uncertainty of measurement

Uncertainty of measurement shall be expressed in appropriate terms for the assigned value of each measurable quantity pertaining to a reference material.

NOTE   The principles given in the 'Guide to the expression of uncertainty in measurement' (GUM:1993) preferably should be followed. The assigned value, y, and related expanded uncertainty, U, (or combined standard uncertainty, $u_c(y)$) pertaining to a measurable quantity characterizing the reference material should be stated. The minimum information should be:

(numerical value of y ± numerical value of U) unit,

where $U = u_c(y) \times k$, with the coverage factor $k = 2$, giving a level of confidence of approximately 95 %.

7   Validation of metrologically traceable calibration

7.1 The following conditions shall apply to the concept of metrologically traceable calibration:

a)   The reference and routine measurement procedures measure the same quantity.

b)   The mathematical relationship between the measurement results generated by the routine procedure and the measurement results generated by a higher order measurement procedure, is the same for all relevant human samples.

c)   The mathematical relationship between the measurement results generated by the measurand in a given calibrator using the reference and the routine procedure is the same as the relationship expected for measurands in routine human samples. This assumption has been termed commutability of the reference material (see 3.9).

NOTE 1   The object of the use of metrologically traceable calibrators in routine measurement procedures, such as those of in vitro diagnostic medical devices, is to produce a result of measurement of the measurand that is as close as required to that which would have been obtained if the reference measurement procedure to which the calibrators are metrologically traceable had been applied to the same samples. Thus, the trueness of results given by a calibrated routine measurement procedure derives from that of the reference measurement procedure when such is available.

NOTE 2   When the conditions a), b), and c) do not apply, the use of a manufacturer's product calibrator with assigned value cannot guarantee that the routine results are metrologically traceable to the reference measurement procedure.

7.2 The commutability of the manufacturer's working calibrator(s) (see 4.2.2 g)) shall be assessed by the manufacturer applying both reference measurement procedure (see 4.2.2 b) or d)) and the routine measurement procedure (see 4.2.2 j)) to the manufacturer's working calibrator and to a set of relevant human (routine) samples.

If the mathematical relationship between the results of the reference measurement procedure, x, and the results of the routine measurement procedure, y, for the human samples is not significantly different from that found for the manufacturer's working calibrator(s), then commutability of the calibrator shall have been demonstrated.

NOTE   If the spread of the points, (x, y), around the regression line and/or its offset are unacceptable, the reason for this outcome can be a difference in analytical specificity between the two measurement procedures.

7.3 The commutability of the manufacturer's product calibrator, shall be demonstrated by comparing the results of measurements, made by both the reference procedure and the calibrated routine procedure on a set of actual samples of a type to which the routine measurement procedure is intended to be applied.

NOTE 1   For subdivided or successive production batches of a product calibrator, full validation can be made initially and then to a reduced extent for subsequently released portions if sufficient portion-to-portion homogeneity and stability can be demonstrated.

The samples shall be authentic, preferably single-donation and unspiked human samples and shall have values as evenly distributed as practicable over the whole of the specified measuring interval for the type of quantity.

NOTE 2   Spiking should only be allowed if the resulting sample mimics natural samples.

7.4 Replicate measurements shall be made on each sample by the reference and calibrated routine procedures. For metrological traceability to be achieved, the results by the routine procedure shall be related to those of the reference procedure by, e.g. a linear regression of unit slope and zero intercept with a stated probability.

NOTE   If linear regression is used, the observed value of the slope should be stated, including its uncertainty.

A unit slope is expected but a deviation from unit slope within a stated interval of quantity values may be tolerable. In a particular case, tolerance limits (as distinct from uncertainty of measurement) will depend on the state of development of methods of measurement and the medical uses to which the results are to be applied.

The observed value of the intercept should be stated. If a value significantly different from zero at a given probability is considered tolerable, the reasons for this shall be stated. If a correction is introduced, its derivation and use shall be available upon request. The uncertainty of the value assigned to the manufacturer's product calibrator shall be augmented by the uncertainty of the correction, if significant. An intercept on the axis of the routine measurement procedure significantly different from zero can indicate a difference of analytical specificity between the two procedures, which could invalidate the principle of metrological traceability.

The expected variability of comparison around the regression line (prediction limits) may be estimated at a given probability on the basis of the number of samples and the respective uncertainties of the two measurement procedures. Variations greater than this indicate an aberrant-sample-dependent variability in the inter-procedure relationship that invalidates metrologically traceable routine results for certain samples. Alternatively, a limit of maximum allowable relative variation between results by the reference and calibrated routine procedures may be specified by the manufacturer. Variations below and including this limit shall be taken to indicate acceptable constancy of the inter-procedure relationship.

7.5 If a panel of human samples is used as part of the process of assigning a value to the manufacturer's product calibrator, the same panel shall not be used also to validate metrological traceability.

8   Information on metrological traceability to be given in the instructions for use of an in vitro diagnostic medical device

EN 375:2001 (especially 5.16) applies. The uncertainty of the assigned values of calibrators and trueness control materials shall be provided on request to the professional end-user, when available.

Information shall also be given on the commutability of the product calibrator as regards the measurement procedure which assigned the value to the material and the end-users' routine measurement procedure for which the material is intended.

NOTE   Details of the transfer protocol for the product calibrator will be included in the product-related Technical Documentation.

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