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

Dispositifs médicaux de diagnostic in vitro — Mesurage des grandeurs dans les échantillons d'origine biologique — Exigences relatives aux matériaux de référence certifiés et au contenu de la documentation associée

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Foreword

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

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 15194 was prepared by the European Committee for Standardization (CEN) Technical Committee CEN/TC 140, In vitro *diagnostic medical devices*, 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).

This second edition cancels and replaces the first edition (ISO 15194:2002), which has been technically revised.

Introduction

Reference measurement systems are needed to produce useful and reliable measurement results, whether in science, technology or routine service, so as to be comparable and ultimately metrologically traceable to measurement standards and/or measurement procedures of the highest metrological level.

Substances or devices that are used to obtain this metrological traceability, through time, distances and different measurement procedures, are reference materials. Certified reference materials are needed at the higher metrological levels of a calibration hierarchy.

A given certified reference material is supported by documentation containing sources of material, descriptions, measurement results, metrological traceability, instructions for use, stability data and storage conditions, as well as health and safety warnings. This International Standard specifies the quality requirements for such materials and the content of their supporting documentation.

Reference materials are used for one of three main purposes:

a) calibration of quantity values indicated by a measuring system or assigned to another reference material;

b) validation or control of trueness of measured values in a given laboratory, or in a group of laboratories;

NOTE In ISO terminology "trueness" is related to "bias", "systematic effect" and "systematic error", whereas "accuracy" is related both to "trueness" (with its relations) and "precision", where the latter is related to "standard deviation", "coefficient of variation ", "random effect" and "random error".

c) evaluation of the performance of a new measurement procedure.

The maximum acceptable measurement uncertainty of the assigned value of a reference material depends on the requirements of the measured quantity values obtained by a measurement procedure involving the reference material.

As the proper use of a reference material depends on its description, it is important to apply rules for the documentation of reference materials.

The advantages of having standards available are listed in ISO/IEC Guide 15.

In Clause 3 of this International Standard, concepts are indicated by *italicized text*.

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

1 Scope

This International Standard specifies requirements for certified reference materials and the content of their supporting documentation, in order for them to be considered of higher metrological order in accordance with ISO 17511. It is applicable to certified reference materials classifiable as primary measurement standards, secondary measurement standards and international conventional calibrators that function either as calibrators or trueness control materials. This International Standard also provides requirements on how to collect data for value determination and how to present the assigned value and its measurement uncertainty.

This International Standard applies to certified reference materials with assigned values of differential or rational quantities. Annex A provides information on nominal properties and ordinal quantities.

This International Standard does not apply to reference materials that are parts of an *in vitro* diagnostic measuring system, although it is possible that many elements are helpful.

2 Normative references

The following referenced documents are indispensable for the application 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 31 (all parts)[1)], *Quantities and units*

ISO 5725-2, *Accuracy (trueness and precision) of measurement methods and results — Part 2: Basic method for the determination of repeatability and reproducibility of a standard measurement method*

ISO 17511:2003, In vitro *diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials*

ISO 18153, In vitro *diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values for catalytic concentration of enzymes assigned calibrators and control materials*

ISO Guide 31, *Reference materials — Contents of certificates and labels*

ISO Guide 34, *General requirements for the competence of reference material producers*

ISO Guide 35, *Reference materials — General and statistical principles for certification*

ISO/IEC Guide 98-3:2008, *Guide to the expression of uncertainty in measurement (GUM:1995)*

ISO/IEC Guide 99:2007, *International vocabulary of metrology — Basic and general concepts and associated terms (VIM)*

1) The ISO 31 series is currently being replaced progressively by the ISO 80000 series and the IEC 80000 series.

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/IEC Guide 99 and the following apply.

3.1
primary measurement standard
primary standard
measurement standard whose quantity value and measurement uncertainty are established using a primary measurement procedure

EXAMPLE Primary measurement standard of amount-of-substance concentration prepared by dissolving a known amount of substance of a chemical component to a known volume of solution.

NOTE 1 Adapted from ISO/IEC Guide 99:2007, 5.4.

NOTE 2 The concept of “primary measurement standard” is equally valid for base quantities and derived quantities.

NOTE 3 Further explanation of the role of primary measurement standards within a calibration hierarchy can be found in ISO 17511 and ISO 18153.

3.2
secondary measurement standard
secondary standard
measurement standard whose quantity value and measurement uncertainty are assigned through calibration with respect to a primary measurement standard for a quantity of the same kind

NOTE 1 The relation can be obtained directly between the primary measurement standard and the secondary measurement standard, or involve an intermediate measuring system calibrated by the primary standard and assigning a measurement result to the secondary standard.

NOTE 2 Adapted from ISO/IEC Guide 99:2007, 5.5.

EXAMPLE NIST Standard Reference Material 1951b, Lipids in Frozen Human Serum is a secondary measurement standard that is calibrated using NIST Standard Reference Material 1911c, Cholesterol of known purity.

NOTE 3 “Measurement standard” includes “reference material”.

NOTE 4 Further explanation of the role of secondary measurement standards within a calibration hierarchy can be found in ISO 17511 and ISO 18153.

3.3
international conventional calibrator
international conventional calibration material
calibrator whose quantity value is not metrologically traceable to the SI but is assigned by international agreement

NOTE 1 The quantity is defined with respect to the intended application.

NOTE 2 Adapted from ISO 17511:2003, 3.11.

3.4
reference material
RM
material, sufficiently homogeneous and stable regarding one or more properties, used in calibration, assignment of a value to another material, or quality assurance

NOTE 1 “Reference material” comprises materials embodying quantities as well as nominal properties.

NOTE 2 Adapted from ISO/IEC Guide 99:2007, 5.13.

EXAMPLE 1 Human serum with an assigned quantity value for the amount-of-substance concentration of cholesterol, used only as a calibrator, embodies a quantity.

EXAMPLE 2 DNA compound containing a specified nucleic acid sequence embodies a nominal property.

NOTE 3 In this definition, *value* covers both “quantity value” and “nominal property value”.

NOTE 4 Some reference materials have quantities which are metrologically traceable to a measurement unit outside a system of units. Such materials include those containing antibodies to which International Units (IU) have been assigned by the World Health Organization.

NOTE 5 A reference material is sometimes incorporated into a specially fabricated device, e.g.

— glass of known optical density in a transmission filter holder,

— spheres of uniform particle size mounted on a microscope slide, and

— calibration plate for microtiter plate reader.

3.5
certified reference material
CRM
reference material, accompanied by documentation issued by an authoritative body and referring to valid procedures used to obtain a specified property value with uncertainty and traceability

NOTE 1 Adapted from ISO/IEC Guide 99:2007, 5.14.

EXAMPLE Human serum containing cholesterol with assigned quantity value and associated measurement uncertainty stated in an accompanying certificate, used as calibrator or trueness control material.

NOTE 2 In this definition, *uncertainty* covers both “measurement uncertainty” and “uncertainty of nominal value”, such as for identity and sequence, expressed as probabilities. *Traceability* covers both “metrological traceability” of a quantity value and “traceability of nominal value”.

NOTE 3 “Certified reference material” is a specific concept under “reference material”.

3.6
matrix
⟨material system⟩ components of a material system, except the analyte

3.7
matrix effect
influence of a property of the sample, independent of the presence of the analyte, on the measurement and thereby on the measured quantity value

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

NOTE 2 A matrix effect depends on the detailed steps of the measurement as described in the measurement procedure.

EXAMPLE The measurement of the amount-of-substance concentration of sodium ion in plasma by flame emission spectrometry can be influenced by the viscosity of the sample.

3.8
commutability of a reference material
property of a given reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two measurement procedures, and the relation obtained among the measurement results for other specified materials

NOTE 1 The reference material in question is usually a calibrator and the other specified materials are usually routine samples.

NOTE 2 The measurement procedures referred to in the definition are the one preceding and the one following the reference material (calibrator) in question in a calibration hierarchy.

NOTE 3 Adapted from ISO/IEC Guide 99:2007, 5.15.

3.9
report
document giving detailed information on a reference material, supplementary to that contained in a certificate

4 Systematic format of properties in the supporting documentation of a certified reference material

4.1 Format of properties

4.1.1 System

The system is the material itself or a specified part of the material.

EXAMPLES Reconstituted lyophilized plasma (as a system) for which there is a certified amount-of-substance concentration and measurement uncertainty of 17β-Estradiol (as a component); reconstituted lyophilized haemolysate (as a material) containing Haemoglobin β chains (as a system) for which there is a certified amount-of-substance fraction and measurement uncertainty of N-(1-deoxyfructos-1-yl) haemoglobin β chains (as a component).

4.1.2 Component(s)

Any relevant component(s), also called analyte(s), of the system shall be named according to an internationally accepted nomenclature, including for example any necessary indications of elementary entity, relative molecular mass or molar mass, oxidation state, multiple forms comprised and, for enzymes, the EC number.

EXAMPLES Aliphatic carboxylate(C10 to C26, non-esterified); Fibrinogen(340 000); Iron(II+III); Lactate dehydrogenase (E.C.1.1.1.27) isoenzyme 1; Basic fibroblast growth factor(human, rec. DNA).

4.1.3 Kind-of-quantity

The kind-of-quantity, e. g. mass, amount-of-substance, number fraction, amount-of-substance concentration, shall always be stated. If no simple relationship between component and system can be expressed, reference shall be made to the measurement procedure.

NOTE Appropriate names and symbols for kind-of-quantities are given in ISO 31 and in publications by IFCC and IUPAC.

4.1.4 Quantity value

4.1.4.1 If the property is a differential quantity (e.g. Celsius temperature) or a rational quantity (e.g. thermodynamic temperature), it shall have a value consisting of a product of numerical value and measurement unit, together with a measurement uncertainty.

4.1.4.2 The number of significant figures of a quantity value shall be chosen so that the measurement uncertainty lies on the last or, if the first significant figure of the uncertainty measure is 1 or 2, on the two last figures. For numerical values with more than four figures on either side of the decimal mark, these should be separated by a space in groups of three, counting from the mark to the left or right.

4.1.4.3 The measurement unit chosen shall be an SI unit, whenever possible, or other internationally accepted measurement unit.

4.1.4.4 The measurement uncertainty shall be calculated and expressed consistent with ISO/IEC Guide 98-3.

4.2 Construction of systematic designations

A systematic name and value shall consist of elements as specified in 4.1.

EXAMPLE 1 A systematic name of a calibrator for a haematology analyser can be secondary reference material for calibration (Responsible body NN; Product no 4132), for example:

— Erythrocytes; number concentration = (4,71 ± 0,09) 10^{12}/l; average and expanded uncertainty ($k = 2$, with level of confidence 0,95);

— Leukocytes; number concentration = (6,52 ± 0,25) 10^{9}/l; average and expanded uncertainty ($k = 2$, with level of confidence 0,95);

— Thrombocytes; number concentration = (240 ± 12) 10^{9}/l; average and expanded uncertainty ($k = 2$, with level of confidence 0,95).

EXAMPLE 2 Certified reference material (Human serum; BCR; CRM 303)--Calcium(II); amount-of-substance concentration (reconstituted) $c = 2{,}472$ mmol/l ($U = 0{,}019$ mmol/l; $k = 2$), where U is the expanded uncertainty of measurement using the coverage factor k.

4.3 Trivial names

A trivial name shall be constructed by omitting from the systematic name elements that are not necessary for the understanding of the function of the CRM in the measurement.

EXAMPLE The trivial name in general form for the material given in 4.2, EXAMPLE 1, can be:

— “Calibrator(Responsible body NN; Product no 4132)--Erythrocytes, Leukocytes and Thrombocytes”; or

— “Calibrator(Responsible body NN; Product no 4132)--Blood cells”.

The trivial name for the corresponding industry product can be:

— “Calibrator(Company NN; Product no 4132; Batch no 4132-2)--Blood cells”.

5 Properties, production, and characterization of a certified reference material

5.1 Hierarchical position

“Reference material” is regarded as a type of “measurement standard”, and reference materials of higher metrological order shall be classified as measurement standards, in accordance with their positions in the reference measurement system for a given quantity as given in ISO 17511:

a) primary measurement standard (see 3.1);

b) secondary measurement standard (see 3.2);

c) international conventional calibrator (see 3.3).

5.2 Properties

A CRM shall have metrological and commutability properties, allowing it to act as a higher metrological order measurement standard within a calibration hierarchy, or as a trueness control material of higher metrological order as defined in ISO 17511 or ISO 18153.