International Standard

ISO 15193

In vitro diagnostic medical devices — Requirements for reference measurement procedures

Dispositifs médicaux de diagnostic in vitro — Exigences relatives aux procédures de mesure de référence

Third edition
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Foreword

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This document was prepared by Technical Committee ISO/TC 212, *Medical laboratories and in vitro diagnostic systems,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 140, *In vitro diagnostic medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This third edition cancels and replaces the second edition (ISO 15193:2009), which has been technically revised.

The main changes are as follows:

— incorporated requirements, concepts and definitions for consistency with ISO 17511, ISO 15194, and ISO 15195;

— adapted content to make the document applicable to all types of measurands;

— revised Clause 4 to present requirements more transparently;

— added 4.1 added to emphasize quality requirements for a reference measurement procedure (MP);

— updated and summarized aspects of validation in 4.15.

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

Reference measurement systems are needed to enable the results produced by end user measurement procedures (MPs) to be metrologically traceable to either measurement standards, or measurement procedures, or both of the highest metrological level. Such systems exist within a metrological traceability chain/calibration hierarchy as described in ISO 17511. In the context of in vitro diagnostic (IVD) medical devices, traceability to the highest metrological level reduces the risk of harm to patients by avoiding inconsistent results from different measuring systems.

Reference measurement procedures play a crucial role in this metrological traceability system, because they can be used for the following:

a) assessing performance properties of measuring systems – comprising measuring instruments, auxiliary equipment as well as reagents,

b) assessing whether there is a functional interchangeability of different end user measurement procedures purporting to measure the same quantity,

c) assigning quantity values to reference materials that are then used for purposes of calibration or measurement trueness control of measurement procedures, and

d) detecting analytical influence quantities in biological samples measured using end user measurement procedures.

For medical laboratory measurements, in particular, it is important to both patient care and health screening that the measurement results reported by different end user measuring systems be equivalent, comparable over time, reproducible and accurate. Establishing metrological traceability of an end user measuring system to a reference measurement procedure enables equivalent results to be reported. A reference measurement procedure should be specified, especially when

— it is required by e.g. standards, technical specifications, or technical regulations,

— quantity values are to be stated by the manufacturer, and

— technical requirements have a direct relationship to the performance of a product or process.

In vitro diagnostic medical devices — Requirements for reference measurement procedures

1 Scope

This document specifies requirements for reference measurement procedures (RMP) for measurands used in laboratory medicine.

This document applies to:

a) RMPs providing values of differential or rational quantities where each quantity value is a numerical value multiplied by a measurement unit. Annex A provides information on ordinal quantities and nominal properties;

b) any person, body or institution developing RMPs for measurands used in laboratory medicine.

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

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

ISO 15194, *In vitro diagnostic medical devices — Requirements for certified reference materials and the content of supporting documentation*

ISO 17511:2020, *In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/IEC Guide 99, ISO 15194, and ISO 17511 and the following apply.

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

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

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

3.1
analyte
component represented in the name of a measurable *quantity* (3.31)

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 full phrase describes the *measurand* (3.18).

[SOURCE: ISO 17511:2020, 3.1]

3.2
analytical portion
portion of material taken from the *analytical sample* (3.3) and on which the measurement is actually carried out, either directly or following dissolution

Note 1 to entry: The analytical portion is taken directly from the *primary sample* (3.30) or *laboratory sample* (3.15) if no preparation of these is required. The analytical portion is sometimes dissolved to give an *analytical solution* (3.6) before being exposed to the measuring device.

3.3
analytical sample
sample prepared from the *laboratory sample* (3.15) and from which *analytical portions* (3.2) can be taken

Note 1 to entry: The analytical sample can be subjected to various treatments before an analytical portion is taken.

3.4
analytical selectivity
selectivity of a measuring system
selectivity
property of a *measuring system* (3.27), used with a specified *measurement procedure (MP)* (3.23), whereby it provides measured *quantity* (3.31) values for one or more *measurands* (3.18) such that the values of each measurand are independent of other measurands or other quantities in the phenomenon, body, or substance being investigated

[SOURCE: ISO 17511:2020, 3.2, modified — the example and the Notes to entry were removed.]

3.5
analytical sensitivity
quotient of the change in an indication of a *measuring system* (3.27) and the corresponding change in the value of a *quantity* (3.31) being measured

Note 1 to entry: ISO/IEC Guide 99:2007, 4.12 uses the term “sensitivity of a measuring system”.

3.6
analytical solution
solution prepared prior to measurement by dissolving an *analytical portion* (3.2) in a liquid material or dispersing it in a solid material, with or without reaction

3.7
blank
lack of the *analyte* (3.1) or another component necessary to produce an indication of a *measuring system* (3.27) that is specific to the analyte

3.8
calibrator
certified reference material (CRM) (3.10) or *reference material* (*RM)* (3.33) with a traceable assigned *quantity* (3.31) value used in calibration of a *measuring system* (3.27) according to a specified *measurement procedure* (*MP)* (3.23)

[SOURCE: ISO 17511:2020, 3.6, modified — in the definition, “measurement standard” was changed to “CRM or RM with a traceable assigned quantity value”.]

3.9
carry-over
contamination from one *analytical portion* (3.2) to the next

3.10
certified reference material
CRM
reference material RM (3.33), accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated uncertainty and traceability using valid procedures

EXAMPLE Human serum with an assigned *quantity* (3.31) value and associated *measurement uncertainty* (3.26) for concentration (amount of substance per unit volume) of cholesterol inherently present in the serum and used as a *calibrator* (3.8) or as a trueness *control material* (3.11).

Note 1 to entry: "Documentation" is given in the form of a reference material certificate and a certification report.

Note 2 to entry: Requirements for the production and characterization of CRM are given in ISO 17034 and ISO 15194. ISO 33405[1)] provides technical guidance on the characterization and the assessment of the homogeneity and stability of a CRM.

Note 3 to entry: In this definition, "uncertainty" covers both 'measurement uncertainty' and 'uncertainty associated with the value of a nominal property', such as for identity or sequence. "Traceability" covers both '*metrological traceability* (3.28) of a quantity value' and 'traceability of a nominal property'.

Note 4 to entry: Specified quantity values of CRMs require metrological traceability with associated measurement uncertainty.

Note 5 to entry: Specific requirements for CRMs and the content of supporting documentation (in the field of in vitro diagnostic (IVD) medical devices) are given in ISO 15194.

Note 6 to entry: For a specified material, a calibration certificate provided by an accredited calibration laboratory is not by itself sufficient to confer the status of CRM on these types of materials.

[SOURCE: ISO 17511:2020, 3.9, modified — in Note 1 to entry, "certification report" was added; Note 2 to entry was changed; the original Note 5 to entry was deleted and Notes 6 and 7 were renumbered as Notes 5 and 6; in Note 6 to entry, "does not confer" was changed to "is not by itself sufficient to confer".]

3.11
control material
substance, material or artefact intended by its producer to be used to verify the performance of a *measurement procedure (MP)* (3.23)

Note 1 to entry: The control material should be a *certified reference material(CRM)* (3.10), if available.

[SOURCE: ISO 17511:2020 3.11, modified — Note 1 to entry was added.]

3.12
examination
set of operations having the objective of determining the numerical value, text value or characteristics of a property

Note 1 to entry: An examination may be the total of a number of activities, observations or measurements required to determine a value or characteristic.

Note 2 to entry: Laboratory examinations that determine a numerical value of a property are called "quantitative examinations"; those that determine the characteristics of a property are called "qualitative examinations".

[SOURCE: ISO 15189: 2022, 3.8, modified — Note 3 to entry was removed.]

3.13
influence quantity
quantity (3.31) that, in a direct measurement, does not affect a quantity that is actually measured, but affects the relation between the indication and the measurement result

[SOURCE: ISO/IEC Guide 99:2007, 2.52, modified — the examples and the Notes were removed.]

1) Updated reference: ISO 33405 replaced ISO Guide 35, which has been withdrawn.