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

Dispositifs médicaux de diagnostic in vitro — Mesurage des grandeurs dans des échantillons d'origine biologique — Exigences relatives au contenu et à la présentation des procédures de mesure de référence

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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 15193 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 15193:2002), 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 units and/or measurement standards and/or measurement procedures of the highest metrological level. Reference measurement procedures play a crucial role in this metrological system because they can be used for the following:

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

b) in demonstrating if there is a functional interchangeability of different routine measurement procedures purporting to measure the same quantity,

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

d) in detecting analytical influence quantities in patient samples.

For medical laboratory measurements, in particular, it is vitally important to both patient care and health screening that the measurement results reported to the physicians and patients are adequately comparable, reproducible and accurate. In some cases, it is advisable that a reference measurement procedure be given in the form of a standard, namely when it is related to technical requirements:

— that are specified in standards, technical specifications, or technical regulations, etc.,

— for which quantity values are to be stated by the supplier, and

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

The advantages of having such a standard 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 content and presentation of reference measurement procedures

1 Scope

This International Standard specifies requirements for the content of a reference measurement procedure for *in vitro* diagnostic medical devices and medical laboratories.

NOTE 1 It is intended that an experienced laboratory worker who follows a measurement procedure written in accordance with this International Standard can be expected to produce measurement results with a measurement uncertainty not exceeding the stipulated interval.

This International Standard applies to reference measurement procedures providing values of differential or rational quantities. Annex A provides information on nominal properties and ordinal quantities.

This International Standard is valid for any person, body or institution involved in one of the various branches of laboratory medicine whose intention is to write a document to serve as a reference measurement procedure.

Full descriptions of measurement methods are usually published in scientific literature, in which methods are described in sufficient detail that they can be used as the basis of a documented measurement procedure.

NOTE 2 In this International Standard, "international measurement standard" designates a material standard. The term "international standard" is used by WHO for reference materials.

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

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)*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/IEC Guide 99 and ISO/IEC Guide 98-3 and the following apply.

3.1
primary sample
collection of one or more parts initially taken from a system and intended to provide information about the system, or to serve as a basis for a decision about the system

NOTE In some cases, the information provided also applies to a larger system or a set of systems, of which the sampled system is an element.

3.2
laboratory sample
primary sample, or a subsample of it, as prepared for sending to or as received by the laboratory and intended for measurement

3.3
analytical sample
sample prepared from the laboratory sample and from which analytical portions can be taken

NOTE The analytical sample can be subjected to various treatments before an analytical portion is taken.

3.4
analytical portion
portion of material taken from the analytical sample and on which the measurement is actually carried out, either directly or following dissolution

NOTE The analytical portion is taken directly from the primary sample or laboratory sample if no preparation of these is required. The analytical portion is sometimes dissolved to give an analytical solution before being exposed to the measuring device.

3.5
analytical solution
solution prepared prior to measurement by dissolving an analytical portion in a liquid or solid material, with or without reaction

3.6
matrix
〈material system〉 components of a material system, except the analyte

3.7
reference measurement procedure
measurement procedure accepted as providing measurement results fit for their use in assessing measurement trueness of measured quantity values obtained from other measurement procedures for quantities of the same kind, in calibration, or in characterizing reference materials

NOTE 1 Adapted from ISO/IEC Guide 99:2007, 2.7.

NOTE 2 The roles of reference measurement procedures are detailed in ISO 17511 and ISO 18153.

NOTE 3 In ISO terminology, *trueness* is related to *bias*, *systematic effect* and *systematic error*, whereas *accuracy* is related to both *trueness* (with its relations) and *precision*, which itself is related to *standard deviation*, *random effect* and *random error*.

NOTE 4 The term “reference measurement procedure” is intended to be understood as a *measurement procedure of higher order*.

3.8
analytical sensitivity
quotient of the change in an indication and the corresponding change in the value of a quantity being measured

NOTE 1 The term “analytical sensitivity” is not intended to be used as a synonym for “detection limit”.

NOTE 2 ISO/IEC Guide 99:2007 uses the term “sensitivity of a measuring system”.

3.9
analytical specificity
ability of a measurement procedure to determine solely the quantity it purports to measure

3.10
analytical interference
systematic effect on a measurement caused by an influence quantity which does not by itself produce an indication, but which causes an enhancement or depression of the indication

3.11
influence quantity
quantity 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

NOTE Adapted from ISO/IEC Guide 99:2007, 2.52.

3.12
measurand
quantity intended to be measured

NOTE 1 Adapted from ISO/IEC Guide 99:2007, 2.3.

NOTE 2 The term “analyte” is not intended to be used for *measurand*. *Analyte* is a component of a *measurand*.

EXAMPLE In the designation “Blood—Glucose; amount-of-substance concentration”, the term “Glucose” designates the *analyte*, equal to the *component*.

3.13
detection limit
limit of detection
measured quantity value, obtained by a given measurement procedure, for which the probability of falsely claiming the absence of a component in a material is β, given a probability α of falsely claiming its presence

NOTE 1 IUPAC recommends default values for α and β equal to 0,05.

NOTE 2 The abbreviation LOD is sometimes used.

NOTE 3 The term “sensitivity” is discouraged for this concept.

NOTE 4 Adapted from ISO/IEC Guide 99:2007, 4.18.

3.14
calibrator
measurement standard used in calibration

NOTE Adapted from ISO/IEC Guide 99:2007, 5.12.

4 Presentation of a reference measurement procedure

4.1 Elements of a reference measurement procedure

The content of a reference measurement procedure shall comprise at least the elements listed as mandatory in Table 1. The order of the elements may be changed and additional elements, such as an abstract, may be added as appropriate.

Table 1 — Elements of the content of a reference measurement procedure

Element	Type	Subclause in this International Standard
Title page	Mandatory	—
Contents list	Optional	—
Foreword	Optional	—
Warning and safety precautions	Mandatory	4.2
Introduction	Optional	4.3
Title of reference measurement procedure	Mandatory	—
Scope	Mandatory	4.4
Normative references	Optional	—
Terms, definitions, symbols, and abbreviated terms	Optional	4.5
Measurement principle and method	Mandatory	4.6
Check list	Optional	4.7
Reagents	Mandatory	4.8
Apparatus	Mandatory	4.9
Sampling and sample	Mandatory	4.10
Preparation of measuring system and analytical portion	Mandatory	4.11
Operation of measuring system	Mandatory	4.12
Data processing	Mandatory	4.13
Analytical reliability	Mandatory	4.14
Special cases	Optional	4.15
Validation by inter-laboratory comparisons	Mandatory	4.16
Reporting	Mandatory	4.17
Quality assurance	Mandatory	4.18
Bibliography (Annex)	Optional	4.19
Dates of authorization and revision	Mandatory	4.20

4.2 Warning and safety precautions

Attention shall be drawn to any danger associated with a type of sample, reagent, equipment or activity, and all necessary precautions shall be described, including precautions for disposal. Regional, national and local legislation and regulations may apply.

NOTE For a reference measurement procedure that is intended to be presented as an International Standard, refer to ISO 78-2.

4.3 Introduction

The introduction shall comprise the following items, as appropriate, in any order:

a) description of the quantity measured by the reference measurement procedure, in terms of system, component and kind-of-quantity, including any specifications to each;

b) brief statement of the role of the quantity in health care, if appropriate;

c) measurement method and rationale for its choice;

d) measurement model in terms of the measurand as a function of all input quantities;

e) place in a hierarchy of measurement procedures and calibrators;

f) metrological traceability.

4.4 Scope

The scope shall define the subject and aspect(s) covered, indicating any known limits of applicability. This element shall not contain requirements.

The scope should include the following items:

a) objectives of measurement for which the reference measurement procedure is suited;

b) types of sample material to which the reference measurement procedure applies and whether limitations exist;

c) interfering components, such as drugs, metabolites, additives, microbial growth;

d) mention of allowable modifications to the basic reference measurement procedure, e.g. as necessary to eliminate an unusual and identifiable interference [details of modified procedure to be given in a separate clause “Special cases” (see 4.15)];

e) measurement interval.

4.5 Terms, definitions, symbols and abbreviated terms

4.5.1 Concepts

If appropriate, this clause shall describe all elements essential for the understanding of the reference measurement procedure.

NOTE These can include, for example:

a) a system of related concepts, e.g. isoenzymes of lactate dehydrogenase according to electrophoretic mobility,

b) a term that can be used with special meaning, unfamiliar to some potential readers, e.g. “quantity”, “property” or “amount of substance” for the base kind-of-quantity with the unit mole, and

c) a current term that cannot be used for a given reason, e.g. “parts per million (ppm)” is avoided in favour of “mass fraction, in milligram per kilogram” or “volume fraction, in cubic centimetre per cubic metre (or microlitre per litre)” (see also 4.8.4).