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Laboratory medicine — Requirements for reference measurement laboratories

Médecine de laboratoires — Exigences pour les laboratoires réalisant des mesurages 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 15195 was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*.

Introduction

The general requirements for the competence of calibration laboratories are laid down in ISO/IEC 17025 for testing and calibration laboratories. This International Standard refers to the specific aspects of calibration laboratories in the field of laboratory medicine where such “calibration laboratories” are usually denoted as “reference measurement laboratories.”

The results produced by medical laboratories should be traceable to reference materials and/or reference measurement procedures of higher order, whenever these are available. This is necessary in order to allow transferability of measurement results in patient samples irrespective of the place and time of measurement.

In order to achieve this goal, the first and essential step is to define the quantity to be measured. Once the quantity has been defined, a reference measurement system should be established, consisting of

- reference materials,
- reference measurement procedures, and
- reference measurement laboratories.

The reference measurement laboratories should be embedded in international (global) networks organized under the auspices of, for example, International Federation of Clinical Chemistry and Laboratory Medecine (IFCC) and International Committee of weights and Measures (CIPM).

Reference measurement laboratories must operate with a traceability to the highest metrological level available and with a lower uncertainty than routine laboratories. The metrological level of the results provided by reference measurement laboratories should be appropriate to enable routine laboratories to fulfil medical requirements. The specific requirements of medical laboratories carrying out routine measurements are addressed in ISO 15189.

The presentation of reference measurement procedures and the description of reference materials are the subject of ISO standards (ISO 15193 and ISO 15194, respectively). This International Standard describes the performance characteristics required for reference measurement laboratories in laboratory medicine. These are highly specialized laboratories often attached to or subcontracted by entities such as national metrology institutes, quality assessment/proficiency testing organizations, academic centres, or *in vitro* diagnostic medical device manufacturers.

Reference measurement laboratories should implement reference measurement procedures and produce results of measurement that are accurate and traceable to national or international primary reference materials when such are available. Whenever possible, traceability should be established to a reference material which forms an embodiment of the SI unit (ISO 17511).

In many instances, properties of biological materials cannot be expressed in SI units as the molecular structure of their analytes is not exactly known and may be different in a reference material from that in a native sample of human origin (e.g. state of glycosylation of a protein); then the traceability chain ends at a lower level, e.g., at an arbitrary international unit (int. unit). However, the reference measurement laboratory should provide traceable values on reference materials supplied by customers to the highest available level of reference measurement procedures or reference materials.

Even if the value for a property of a biological material is not traceable to an SI unit, each step of a reference measurement procedure (e.g. gravimetry, volumetry, temperature measurement) should have values that are traceable to the respective SI unit.

The traceability concept, its applicability and limitations are described in detail in the standard “Metrological traceability of values assigned to calibrators and control materials” (ISO 17511).

Further tasks of reference measurement laboratories may include upon request:

— assisting in investigation of new or existing measurement procedures with regard to their trueness,

— providing accurate (true and precise) assigned values with stated uncertainty to materials for calibration, internal quality control, and external quality assessment,

— acting as consultants to government, industry, and organizations conducting external quality assessment schemes as well as to specialized individual laboratories.

The requirements described in this document and in ISO/IEC 17025 are prerequisites for reference measurement laboratories to perform their tasks adequately. When the reference measurement laboratory is integrated into a routine laboratory, the management system, personnel and equipment requirements of the reference laboratory should comply with this International Standard and be independent of the routine laboratory.

This International Standard should aid in establishing confidence in reference measurement laboratories that are able to demonstrate their competence in accordance with the requirements laid down here.

This International Standard may form a basis for the accreditation of a reference measurement laboratory that applies for official recognition of the performance of a reference measurement procedure. Reference measurement laboratories are usually accredited by the national metrology institutes or national accrediting bodies.

NOTE The requirements for recognition and operation are set out in ISO/IEC Guide 58. The International Laboratory Accreditation Cooperation (ILAC) coordinates and supervises the regional organizations of national accrediting bodies, such as the European Cooperation for Accreditation (EA), which ensures that member bodies recognize each other's accreditation certificates.

This International Standard may furthermore facilitate collaboration between reference measurement laboratories performing interlaboratory comparisons and encourage the highly desirable formation of international networks of reference measurement laboratories.

It is understood that reference measurement procedures should be of high metrological order and the analytical principle of measurement applied should allow an adequately low uncertainty. The results of reference measurements should be traceable to reference materials or to a reference procedure of higher order when available.

Laboratory medicine — Requirements for reference measurement laboratories

1 Scope

This International Standard gives the specific requirements for reference measurement laboratories in laboratory medicine. Examinations of properties with results reported on a nominal or ordinal scale are not included.

This International Standard is not applicable to routine medical laboratories.

NOTE 1 It is the laboratory's responsibility to comply with the relevant legal health and safety requirements.

NOTE 2 Requirements for routine medical laboratories are specified in ISO 15189.

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 15193, *In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Presentation of reference measurement procedures*

ISO 15194:2002, *In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Description of reference materials*

ISO 17511, *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 assigned values for catalytic concentration of enzymes in calibrators and control materials*

International vocabulary of basic and general terms in metrology (VIM). BIPM, IEC, IFCC, ISO, IUPAC, IUPAP and OIML, 1993[1)]

Guide to the expression of uncertainty in measurement (GUM). BIPM, IEC, IFCC, ISO, IUPAC, IUPAP and OIML,1993[1)]

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1) This vocabulary 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

3 Terms and definitions

For the purposes of this document, the terms and definitions given in the *International vocabulary of basic and general terms in metrology (VIM)* and the following apply.

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

[VIM:1993, 3.5]

NOTE 1 According to ISO 5725-1, 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 estimate of an inverse measure of accuracy is “deviation”, defined as “value minus a conventional true value”.

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

NOTE 5 In this International Standard the concept “accuracy of measurement” is related to both **trueness of measurement** (3.10) and **precision of measurement** (3.4) whereas the EU Directive on *in vitro* diagnostic medical devices uses the term “accuracy” instead of “trueness”.

3.2
certified reference material
CRM
reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes its 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

[VIM:1993, 6.14]

3.3
measurable quantity
attribute of a phenomenon, body, or substance that may be distinguished qualitatively and determined quantitatively

[VIM:1993, 1.1]

3.4
precision of measurement
closeness of agreement between independent results of measurement obtained under stipulated conditions

NOTE 1 Adapted from ISO 3534-1:1993, 3.14.

NOTE 2 “Precision of measurement” is a qualitative concept.

NOTE 3 The degree of precision is usually expressed numerically by statistical measures of imprecision of measurement such as “standard deviation” and “coefficient of variation” that are inversely related to precision.

NOTE 4 “Precision” of a given measurement procedure is subdivided according to the specified precision conditions. “Repeatability” relates to essentially unchanged conditions and is often termed “within-series precision” or “within-run precision.” “Intermediate precision” refers to conditions where there is variation in one or more of the factors time, calibration, operator, and equipment — usually within a laboratory. “Reproducibility” relates to change in conditions, i.e., different laboratories, operators, and measuring systems (including different calibrations and reagent batches) and is often termed “interlaboratory precision”.

NOTE 5 The definition used in this International Standard is consistent with related ISO standards. The definition for precision of measurement as stated in ISO 3534-1:1993, 3.14, reads as follows: closeness of agreement between independent test results obtained under stipulated conditions.

3.5
reference material
material or substance, one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of a measuring system, the assessment of a measurement procedure, or for assigning values to materials

[VIM:1993, 6.13; ISO Guide 30:1992, 2.1]

3.6
reference measurement laboratory
laboratory that performs a reference measurement procedure and provides results with stated uncertainties

NOTE ISO/IEC 17025 uses the term "calibration laboratory".

3.7
reference measurement procedure
thoroughly investigated measurement procedure shown to have an uncertainty of measurement commensurate with the intended use, especially in assessing the trueness of other measurement procedures for the same quantity and in characterizing reference materials

NOTE 1 Adapted from ISO 15193.

NOTE 2 When several reference measurement procedures exist for a given measurable quantity, it can be possible to arrange them in a hierarchy according to size of uncertainty of measurement. A primary reference measurement procedure is sometimes termed a "definitive method of measurement", but not by VIM:1993.

NOTE 3 The Consultative Committee on Amount of Substance (CCQM) of BIPM has defined a "primary method of measurement" as a method 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 whose results are, therefore, accepted without reference to a standard of the quantity being measured. For amount of substance, the following principles of measurement were identified as suitable for primary measurement procedures: isotope dilution-mass spectrometry, coulometry, gravimetry, titrimetry, and determination of colligative properties such as freezing point depression. BIPM, Comité Consultatif pour la Quantité de Matière, 1995.

NOTE 4 The Analytical Chemistry Division of IUPAC describes an allied concept, "absolute method", wherein calculations are based on universal quantities and fundamental physical constants only.

3.8
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]

3.9
true value of a quantity
value consistent with the definition of a given particular quantity

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 a "true value" because there may be many values consistent with the definition of a given particular quantity.

[VIM:1993, 1.19]

NOTE 4 ISO 3534-1:1993 instead of “a true value,” uses the concept “the accepted reference value,” which can be a theoretical (true), assigned, consensus, or procedure-defined value.

3.10
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 Adapted from ISO 3534-1:1993, 3.12.

NOTE 2 “Trueness of measurement” is a qualitative concept.

NOTE 3 The degree of trueness is usually expressed numerically by the statistical measure “bias” that is Inversely related to trueness.

3.11
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, GUM:1993, B.2.18]

NOTE 1 The parameter may 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 “Uncertainty of measurement” comprises, in general, many components. Some of these components may be evaluated from the statistical distribution of the results of series of measurements and can be characterized by “experimental standard deviations”. The other components, which can also be characterized by standard deviations, are evaluated from assumed probability distributions based on experience or other information.

NOTE 3 It is understood that the result of the measurement is the best estimate of the value of the measurand, and that all components of uncertainty, including those arising from systematic effects, such as components associated with corrections and reference standards, contribute to the dispersion.

3.12
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

[ISO 9000:2000, 3.8.5]

3.13
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

[ISO 9000:2000, 3.8.4]

4 Management system requirements

4.1 Organization and management

The laboratory shall be organized and operated so that its independence of judgement and its integrity shall not be influenced by commercial, financial, or other conflicts of interest.

The laboratory management shall specify the responsibility, authority, and interrelation of all personnel who manage, perform, review and approve work affecting the quality of reference measurements.

The management of the laboratory shall designate a quality manager and nominate a deputy to serve in his or her absence.

4.2 Quality management system

The laboratory shall establish and maintain a quality management system documented in a quality manual. This shall describe the objectives, the quality policies, and quality control programmes which enable the laboratory to assure the quality of its reference measurement results with the stated level of uncertainty of measurement according to the *Guide to the expression of uncertainty in measurement* (GUM).

The contents of the quality manual shall be available to and implemented by the personnel of the laboratory as appropriate.

The quality management system shall consist of the following elements documented in the quality manual:

a) an introduction;

b) a description of the legal identity of the laboratory;

c) a quality policy;

d) an organizational chart, identifying the laboratory within the organization;

e) a description of the within-laboratory organization and distribution of responsibilities of the director and the staff of the laboratory;

f) a description of the premises, services and any environmental control of the laboratory;

g) all safety requirements;

h) a listing of reference materials used;

i) a description of the major equipment of the laboratory and its maintenance and validation procedures;

j) a listing of the quantities for which the laboratory offers reference measurements;

k) documentation in accordance with the requirements of ISO 15193 of reference measurement procedures applied by the laboratory;

l) a description of the internal quality control and external quality assessment procedures;

m) a statement of the metrological services provided by the laboratory;

n) policies and procedures to avoid involvement in any activities that might diminish confidence in its competence, impartiality, judgement, or operational integrity;

o) procedures to be followed for feedback, corrective action, and reporting whenever non-conformity or error is detected;

p) policies and procedures for addressing deviations from approved measurement procedures;

q) procedures for dealing with complaints and for recording resulting actions;

r) procedures for protecting the confidentiality and proprietary rights of a customer;

s) procedures for internal audit and review;

t) a procedure for control and maintenance of documentation;

u) compliance with requirements of regulatory authorities;

v) a statement concerning any accreditation status and accrediting body;

w) a procedure to be followed for signature of certificates.