INTERNATIONAL STANDARD

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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*.

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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

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.

5.3 Production and characterization

A CRM shall be produced in accordance with the quality system requirements set out in ISO Guide 34, and characterized in accordance with the requirements of ISO Guide 35.

The suitability of the CRM for calibration or trueness control purposes shall be assessed by evaluating its commutability, such that it is consistent with its intended use as stated in 6.4.4 and 6.4.9. Relevant information shall be given on the certificate or in supporting documentation.

6 Content of supporting documentation

6.1 Supporting documentation

A CRM shall have a label securely attached to the product packaging of an individual CRM unit.

A CRM shall be accompanied by a certificate. In addition, the CRM may be either accompanied by a certification report, or all the information appropriate to a full certification report shall be obtainable from the CRM producer.

6.2 Label

The information provided on a label should serve only to identify the CRM and should be confined to the name of the producer, the name of the material, the producer's identification code for the material, the batch number if the producer's code is not unique for a certain batch and relevant health and safety warnings. See ISO Guide 31, ISO 18113-2 and existing legislation on labelling of dangerous products.

NOTE 1 It is advisable that the certified property value(s) not be included, in order to prevent the use of the material without the information in the certificate having been studied.

NOTE 2 The label can make use of graphical symbols as given in EN 980.

6.3 Certificate

A certificate should include the items specified in ISO Guide 31. As a minimum, it shall include the following essential items:

a) name of the material;

b) producer and producer's identification code for the CRM with a lot identification, when available;

c) general description of the material;

d) intended use, including information on the commutability of the material consistent with the intended use;

e) information about transport and instructions for appropriate conditions of storage, correct handling, and stability;

f) safety instructions;

g) instructions for proper use;

h) certified property values(s), each accompanied by a statement of measurement uncertainty (if applicable);

i) any indicative values or recommended values;

j) measurement procedure(s) used to obtain property values (with full details where values are dependent on the measurement procedure);

k) date of certification and period of validity, if applicable;

l) reference to any certification report.

6.4 Certification report

6.4.1 General

The information appropriate to a certification report shall comprise at least the elements listed as mandatory in Table 1.

NOTE The order of the elements listed in Table 1 can vary, and additional elements, e.g. an abstract, can be added as appropriate.

Table 1 — Main elements (clauses) of a certification report for a certified reference material

Element	Type	Subclause in this International Standard
Title page	Mandatory	—
Contents list	Optional	—
Foreword	Mandatory	—
Warning and safety precautions	Mandatory	6.4.2
Introduction	Optional	6.4.3
Title of report	Mandatory	—
Scope of application for the CRM	Mandatory	6.4.4
Terms and definitions	Mandatory	—
Symbols and abbreviations	Mandatory	—
Terminology	Optional	6.4.5
General properties	Mandatory	4.1; 6.4.6
Specific properties	Mandatory	4.1; 6.4.7
Characterization	Mandatory	6.4.8
Intended use	Mandatory	6.4.9
Instructions for use	Mandatory	6.4.10
Certifying body	Mandatory	6.4.11
Bibliography	Optional	6.4.12
Annexes	Mandatory	6.4.13
Dates of authorization and revision	Mandatory	6.4.14

6.4.2 Warning and safety precautions

6.4.2.1 Attention shall be drawn to any danger associated with the CRM and its use. All necessary precautions shall be described (see ISO 14971, ISO/IEC Guide 51 and ISO/IEC Guide 63). Regional, national, and local legislation and regulations may apply.

6.4.2.2 Warning and safety precautions for CRMs, which are given in an International Standard, shall be printed in bold type as follows:

a) immediately after the title of the International Standard, if the danger encountered is due to the CRM, e.g. native material of human origin with, in principle, potential infectiveness (but found negative for HIV antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody), radioactive material or a carcinogen;

b) as a cautionary statement, under instructions for use, e.g. for a measurement using equilibration gases (CAVE aerosol formation).

Warning notes and safety precautions shall be unnumbered.

The source text presenting the dangers to health should be quoted, where appropriate.

6.4.3 Introduction

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

a) systematic description of the CRM in accordance with 4.1;

b) names of quantities in the measurement of which the CRM is intended to be used, indicated by system, component, and kind-of-quantity.

6.4.4 Scope of application for the CRM

The clause shall define the subject and aspect(s) covered, indicating limits of applicability.

NOTE The items include as appropriate:

a) current reference measurement procedure(s) or current generally-used routine measurement method(s) or measurement procedure(s) for which the CRM is produced,

b) method(s) of measurement or measurement procedure(s) for which the CRM is known to be unsuitable,

c) influence quantities in the CRM involving, e.g. drugs, metabolites, additives, microbial growth, and

d) mention of major required pre-treatment of the CRM which is not performed on the biological samples according to a specified measurement procedure (e.g. reconstitution of lyophilized material).

6.4.5 Terminology

6.4.5.1 General

This element shall describe the meaning and use of concepts and terms that are specific to the description, unfamiliar to potential readers or chosen among several possibilities for a stated reason.

NOTE The clause “Terminology” is complementary to the clause “Terms and definitions” and sometimes also to the clause “Symbols and abbreviations” (see Table 1); the terms can be incorporated in either or distributed between both.

6.4.5.2 Nomenclature

Terms for measurable quantities, as well as their spelling and structure, shall be taken from the latest recommendations by authoritative sources, preferably relevant international organizations.

Terms for kind-of-quantities, their symbols and units shall be in accordance with International Standards, especially ISO 31.

6.4.5.3 Trivial names

If a trivial name is used, it shall be given in parentheses following the systematic name the first time the systematic name appears in the text.

6.4.6 General properties

6.4.6.1 The origin and nature of the starting material shall be stated.

6.4.6.2 The relevant historical details of the starting material shall be stated, in so far as they influence the properties of the final material to be pooled, e.g. age and sex of donors, temperature and length of storage of blood serum and clot together before separation, storage time and temperature. The safety aspects shall be covered, e.g. the examination of material of human origin for hepatitis B virus surface antigen, hepatitis C virus antibody, HIV antibody and other markers of infectiveness, as stipulated by regulations on each donated portion.

6.4.6.3 Details of sample preparation of the starting material shall be described as necessary for the application of the material. Purification with a check for impurities shall be indicated.

6.4.6.4 The compounds and concentrations or contents of any additives should be specified.

EXAMPLE Additives for CRMs used in the clinical laboratory include anticoagulants, antioxidants, antimicrobial agents, stabilizers, wetting agents and coating of pellets.

NOTE Intellectual property rights and patent considerations can prevent a CRM producer from describing in full detail the preparation of the CRM or the identification of additives.

6.4.6.5 The physical state and phases of the CRM shall be stated, such as lyophilized serum.

6.4.6.6 The estimated within-sample and between-sample homogeneity, with regard to the minimum analytical portion, shall be stated (see 6.4.8.3). The size of sample on which the homogeneity of the CRM has been established shall be stated, and the minimum sample size for use stated.

EXAMPLE A CRM consists of a lyophilized tissue powder filled into vials. The within-vial homogeneity was investigated on three replicate samples, each having a mass of 200 mg, taken from the material in each of 20 vials. The between-vial variation was investigated on one sample of 200 mg from each of 60 vials selected from various positions on the lyophilization plate. The instructions for use states that “the recommended minimum analytical portion has a mass of 200 mg”.

6.4.6.7 If applicable, the physical form shall be described, e.g. shape, dimensions, number and amount.

EXAMPLE A CRM, glass filter for light spectrometry is intended as a reference source for the calibration of the absorbance scale of spectrometers. It consists of three individual filters and one empty filter holder, ($10 \times 10 \times 50$) mm. Each filter bears an identification number. The upper left corner has been removed to indicate correct placing in the metal holder.

6.4.6.8 Any sterilization procedure applied shall be described.

6.4.6.9 The container and/or packaging shall be specified as to type, material, closure and atmosphere.

6.4.6.10 The stability of the CRM shall be stated. Storage conditions for the unopened container shall be given, e.g. temperature, humidity and light. The extent of instability under the prescribed conditions shall be stated. Any future check of stability should be stated. It shall be stated if the CRM is of restricted stability once its container is opened.

A shelf life for the unopened container shall be given.

NOTE Such CRMs are usually supplied in sealed units.

6.4.6.11 The quality systems that were followed during production, characterization, handling, storage and distribution shall be identified, e.g. in accordance with ISO Guide 34, ISO 13485, ISO 15195 or ISO/IEC 17025.

6.4.6.12 Any hazard associated with the CRM or its use shall be stated and appropriate precautions detailed (see 6.4.2).

6.4.7 Specific properties

6.4.7.1 The specific properties of a CRM that influence any quantity for which a value is given shall be described by at least the information specified in 6.4.7.2 to 6.4.7.11.

6.4.7.2 When available, the molecular composition or biological or biochemical functional activity of each relevant component shall be stated, in accordance with 4.2.

6.4.7.3 The quantity to which a value is assigned shall be specified.

6.4.7.4 The purity of the main component in a “pure” CRM shall be stated as mass fraction, volume fraction, amount-of-substance fraction or number fraction. In the case of an unstable component, the date of initial measurement shall be stated along with the rate of decay.

6.4.7.5 The matrix of the material shall be described. For dried and lyophilized materials, the proportion of any solvent residue shall be stated.

6.4.7.6 The quantity for which a value is given shall be adequately stated with indications of system, component and kind-of-quantity, and with relevant specifications to each (see 4.1).

6.4.7.7 Data for the extent of commutability investigated shall be given, e.g. for the concentration of a particular protein.

6.4.7.8 The type of scale on which the value of the property is examined shall be specified, i.e. whether it is a nominal, ordinal, differential (also called interval) or rational scale.

The set of possible values should be given, if required.

EXAMPLE A stabilized blood sample can be used as a reference material for the measurement of the amount-of-substance concentration difference of base-binding groups (“base excess“) in blood, and a differential scale is required (.... –4,2 –4,1 ... –0,1 0,0 +0,1 ... +4,1 +4,2 ....) mmol/l; the amount-of-substance concentration of hydrogen carbonate ion is measured on a rational scale (0,0 0,1 0,2 ....) mmol/l.

6.4.7.9 SI units shall be used wherever possible and appropriate. Where an arbitrary unit is used, it shall have an internationally agreed definition or a definition described by a given measurement procedure.

6.4.7.10 The measurement uncertainty shall be expressed either as a combined standard uncertainty or as an interval derived from an expanded uncertainty with a stated level of confidence. Valid procedures for the evaluation of measurement uncertainty shall be followed, such as those outlined in ISO/IEC Guide 98-3.

NOTE The components of the measurement uncertainty are caused by inhomogeneity of the material and its determination, the instability of the material and its determination, and the value assignment process. The latter is often reflected by analytical variation among laboratories, operators, calibrations of measuring systems, measurement procedures and runs. They comprise systematic as well as random components.

EXAMPLE 1 Certified reference serum (BCR 348 NN, reconstituted)--Progesterone; amount-of-substance concentration $c = (40{,}3 \pm 1{,}0)$ nmol/l; unweighted average and expanded uncertainty ($k = 2$) giving an interval that is estimated to have a level of confidence of 0,95.

EXAMPLE 2 The certified purity of a certain material is stated as relative amount-of-substance content (actual/theoretical) = 0,996 3 (0,993 6; 0,997 5); median (0,25- and 0,75-fractile).

6.4.7.11 The metrological traceability of assigned values of CRMs shall be described.

6.4.8 Characterization

6.4.8.1 General

Technically valid procedures shall be used to characterize and validate a CRM.

6.4.8.2 Planning of experimental design

The certification study shall be described.

NOTE The study will depend on the nature of the CRM and the way in which it will be used. In general, it is advisable that homogeneity and stability be investigated before considering the assignment of values. It is also necessary to decide the maximum permissible measurement uncertainty of an assigned value, because this will influence the design of the study.

6.4.8.3 Assessment of homogeneity

Studies on the homogeneity of the CRM, including within-sample and between-sample homogeneity shall be undertaken, evaluated and reported in accordance with ISO Guide 35.

6.4.8.4 Statistical evaluation of results

A statistical evaluation of the data collected during the study shall be made. The method of evaluation shall be described and shall be consistent with approaches described in ISO Guide 35 and ISO 5725-2.

6.4.8.5 Assessing the stability

The procedures for assessing the stability shall be undertaken, evaluated and reported in accordance with ISO Guide 34 and ISO Guide 35.

NOTE 1 For CRMs, a stability allowing storage life from 8 to 10 years of use is a relevant aim.

The effect of relevant influence properties on stability shall be quantified and documented.

The measurement procedures shall be described, including their calibration and accuracy control.

NOTE 2 Procedures for monitoring the stability of the CRM during its lifetime involve measurement of salient quantities at planned intervals during the time in which the CRM will be used, e.g. measurement of haemoglobin concentration in the plasma of a reference preparation of stabilized blood.

EXAMPLE Vials of the materials are stored at 20 °C, 37 °C, 45 ºC and 56 °C, and measured in duplicate after storage for 110 days, 244 days and 604 days. No statistically significant changes are found ($p > 0{,}05$) in the respective values relative to the values of samples stored at 20 °C, at which temperature the material has been shown to be stable when compared to a sample stored at 70 °C. The material seems sufficiently stable. The stability will be checked during the lifetime of the material.

NOTE 3 The ability to detect eventual instability of a material requires a sufficiently low repeatability coefficient of variation of the measurement procedure.

6.4.8.6 Value assignment

The experimental plan and the measurement procedures used in assigning values shall be described.

NOTE 1 See also ISO Guide 34 and ISO Guide 35.

NOTE 2 The value for a given quantity can be assigned on the basis of one very well documented measurement procedure in one laboratory. In many cases, however, a better foundation is obtained when several experienced laboratories are involved in an interlaboratory comparison at a high metrological level and, if possible, using different measurement methods or even different measurement principles.

6.4.8.7 Quantity value and measurement uncertainty

The quantity value and its measurement uncertainty (based on an uncertainty budget) for each measurement procedure applied shall be reported.

NOTE 1 It is advisable to keep a log describing actually performed adjustment and maintenance of equipment, as well as reports on validation of the measurement procedure and control data.

The following experimental elements shall also be reported:

a) number of replicates within-run;

b) number of runs;

c) number of calibrations;

d) number of different measuring systems for the same purpose.

NOTE 2 Supplementary details are given in ISO Guide 35 and ISO 5725-2.

6.4.8.8 Regional acceptance

Any regional acceptance of the CRM shall be listed.

6.4.9 Intended use

The intended use of the CRM shall be stated.

The CRM can function either as:

a) calibration material (calibrator): to determine the calibration function of a given measurement procedure (which may then also be used to calibrate another reference material); or

b) control material: to assess the measurement bias or measurement uncertainty of an established or new measurement procedure in a given laboratory or in a group of laboratories.

Within a given measuring system in a given laboratory, a CRM shall perform only one of the above functions that shall be specified by the term calibration material (calibrator) or trueness control material.

Known limitations of suitability shall be documented, e.g. when a calibrator or control material intended for use with a particular field measurement procedure gives measurement values that require a correction different from that applied to values on native material (commutability assessment). The instructions for use shall include a statement on the intended use based on validation data on the applicability of the CRM. Application of the CRM outside the scope of intended use implies validation of the CRM by the user for that particular purpose. The recommended statistical treatment of the values obtained by the user shall be indicated for each of the intended uses, at least by reference to literature.

EXAMPLE 1 The measurement uncertainty of a calibration can be calculated from the uncertainty of calibration provided with the assigned value of the calibration material and the repeatability standard deviation of the measurement procedure, taking into account the number of measurements obtained on the calibrator. Formulae for calculation are presented in ISO Guide 33.

EXAMPLE 2 In order to check the precision of a measurement procedure performed in a laboratory, the number of replicate measurements on the CRM is selected according to the acceptable probability of erroneous acceptance or false rejection of the run. The assessment of trueness is made by comparing the average value of examined data with the assigned value taking into account the measurement uncertainties of both. Elimination of outliers is sometimes needed. Formulae for calculation are presented in ISO Guide 33.

EXAMPLE 3 When using the CRM for control of trueness in each analytical run including four determinations on the CRM, one control rule can be that no observation exceeds the $\pm 3 s_r$ limits of acceptance. In this way, a systematic error of $2 s_r$ is detectable with a probability of 0,55 and the probability of false rejection is 0,01. (The repeatability standard deviation of the measurement procedure is symbolized by s_r.)

6.4.10 Instructions for use

6.4.10.1 Safety

The first paragraph of the instructions for use shall contain any cautionary statement (see 6.4.2). Safety precautions concerning equipment, materials, samples and waste shall be included where appropriate in the instructions for use.

6.4.10.2 General

Detailed instructions for use shall be provided, including at least the following information as appropriate:

a) required storage conditions and stability of the CRM as received;

b) opening of the immediate container;

c) required handling of the CRM after opening the immediate container;

d) preparation of sample;

e) techniques for achieving thawing or reconstitution followed by mixing;

f) procedure for obtaining the minimum analytical sample and analytical portion;

g) measurement procedure (either recommended or mandatory);

h) disposal of any remaining material after use.

6.4.10.3 Reagents

If reagents are cited in the instructions for use, each item shall be identified.

6.4.10.4 Accessories

Specified accessories required for use of a CRM shall be listed.

6.4.10.5 Apparatus

Specified apparatus required for use of a CRM shall be listed.

6.4.10.6 Environment

If the use of the CRM requires specific environmental conditions, these shall be stated.

6.4.10.7 Measuring volumes

When necessary, the temperature (and for gases, the pressure) at which a volume is measured shall be specified.

Dilutions prepared by adding one volume of liquid to a volume of another liquid shall be indicated by either:

a) "diluted $V_1 \rightarrow V_2$" if the volume V_1 of the specified solution is diluted in such a way as to give a total volume V_2 of final mixture, e.g. diluted 25 ml $\rightarrow$ 1 l, or

b) "diluted $V_1 + V_2$" if the volume V_1 of the specified solution is added to the volume V_2 of the solvent, e.g. 25 ml + 975 ml.

Expressions such as "V_1:V_2" or "V_1/V_2" shall not be employed, as they are used with different meanings.

6.4.10.8 Reconstitution of lyophilized CRM

Details of reconstitution shall be given.

6.4.10.9 Reference to patented items

If, in exceptional cases, technical reasons justify the preparation of the instructions for use in terms which include the use of items covered by patent rights, it may be necessary to include a notice which draws attention to the fact that it is claimed that compliance with the instructions for use involves the use of a patent.

NOTE For a description of a CRM in an International Standard, see ISO/IEC Directives, Part 1, 2008, 2.14, and ISO/IEC Directives, Part 2, 2004, Annex F.

6.4.11 Certifying body

The name of the certifying body, i.e. the body or organization that accepts responsibility for the information in the supporting documentation, shall be stated and accompanied by the full postal address, telephone and fax numbers and, where available, e-mail address.

6.4.12 Bibliography

Documents which contain additional information, but which are not necessary in order to use the CRM for its intended use, shall be listed in a bibliography.

NOTE 1 This bibliography can take the form of an annex [see 6.4.13 d)]. For a description of a CRM in an International Standard, the bibliography can include referenced documents that are only cited in an informative manner, that have served as background material and that are available upon request. See also ISO/IEC Directives, Part 2.

NOTE 2 The types of publication can comprise, for example, regional and national standards, industrial standards, legal regulations, recommendations issued by international and regional scientific organizations, scientific journal papers, textbooks, manufacturers' standard or product literature and interlaboratory trial reports.

6.4.13 Annexes

Data and information that do not fit into the main part of the report shall be given in annexes.

NOTE Such items can include:

a) data on homogeneity (see 6.4.8.3),

b) data on stability (see 6.4.8.5),

c) data on value assignment (see 6.4.8.6 and 6.4.8.7), and

d) bibliography (see 6.4.12).

6.4.14 Dates of authorization and revision

The dates for the current publication and of any previous edition(s) shall be given.

Annex A
(informative)

Certified reference materials with nominal properties or ordinal quantities

A.1 General

A.1.1 This International Standard states requirements for CRMs of higher metrological order. Each quantity value assigned to such a material, intended for use with measurement procedures, is found on a differential scale or a rational scale, is expressed as a numerical value multiplied by a unit of measurement (see 4.1.4), and is accompanied by a measurement uncertainty.

A.1.2 Other properties than differential or rational quantities may also be defined or reproduced by materials, but the assigned values cannot be expressed by a numerical value multiplied by a unit of measurement. Such values may be found on an ordinal scale or a nominal scale.

A.2 Ordinal quantities and nominal properties

A.2.1 For an ordinal quantity, the values may be phrases or numbers expressing magnitudes of the corresponding properties. The values may be used for ranking by magnitude, but differences and ratios along the scale have no comparative meaning, e.g. a value of “3” or “elevated” assigned to a control solution for dip-sticks giving albumin concentration in urine on a 5-value scale (0, 1, 2, 3, 4 or not elevated, doubtfully elevated, slightly elevated, elevated, strongly elevated).

A.2.2 For a nominal property, the values may be phrases or terms (names) without relation to any magnitude. The values may be arranged in any convenient or conventional order, e.g. a set of terms for types of leukocytes in a control blood smear, or a set of values for blood groups.

A.2.3 The description of CRMs for nominal properties or ordinal quantities should fulfil, as far as possible, the requirements of CRMs for differential and rational quantities as given in this International Standard. Exceptions include:

a) terminological changes of:

   1) quantity to nominal property, also in complex terms, and

   2) measurement to examination for nominal properties, also in complex terms; and

b) technical changes of

   1) the use of values such as those described in A.2.1 and A.2.2,

   2) examination uncertainties expressed as number fractions of misclassification, and

   3) being unable to calibrate in relation to a nominal scale.

The homogeneity and stability of the material shall be demonstrated in view of the relevant properties and quantities.

Bibliography

[1] ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

[2] ISO 14971, *Medical devices — Application of risk management to medical devices*

[3] ISO 15193, In vitro *diagnostic medical devices — Measurement of quantities in samples of biological origin — Requirements for content and presentation of reference measurement procedures*

[4] ISO 15195, *Laboratory medicine — Requirements for reference measurement laboratories*

[5] ISO/IEC 17025, *General requirements for the competence of testing and calibration laboratories*

[6] ISO 18113-2, *Clinical laboratory testing and in vitro diagnostic medical systems — Information supplied by the manufacturer (labelling) — Part 2: In vitro diagnostic reagents for professional use*

[7] ISO/IEC Guide 15, *ISO/IEC code of principles on "reference to standards"*

[8] ISO Guide 30, *Terms and definitions used in connection with reference materials*

[9] ISO Guide 32, *Calibration in analytical chemistry and use of certified reference materials*

[10] ISO Guide 33, *Uses of certified reference materials*

[11] ISO/IEC Guide 51, *Safety aspects — Guidelines for their inclusion in standards*

[12] ISO/IEC Guide 63, *Guide to the development and inclusion of safety aspects in International Standards for medical devices*

[13] ISO/IEC Directives, Part 1, 2008, *Procedures for the technical work*

[14] ISO/IEC Directives, Part 2, 2004, *Rules for the structure and drafting of International Standards*

[15] EN 980, *Graphical symbols for use in the labelling of medical devices*

[16] EA-04/14, *The selection and use of reference materials*, European co-operation for Accreditation, 2003

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