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In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Description of reference materials

Dispositifs médicaux de diagnostic in vitro — Mesure des grandeurs dans les échantillons d'origine biologique — Description des matériaux 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 3.

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 International Standard may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 15194 was prepared by the European Committee for Standardization (as EN 12287:1998) and was adopted, under a special “fast-track procedure”, by Technical Committee ISO/TC 212, *Clinical laboratory testing and* in vitro *diagnostic test systems*, in parallel with its approval by the ISO member bodies.

Contents

Foreword

This European Standard has been prepared by Technical Committee CEN/TC 140 "In vitro diagnostic medical devices", the secretariat of which is held by DIN. International Federation of Clinical Chemistry (IFCC) and the European Confederation of Laboratory Medicine (ECLM) have contributed to its preparation.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by December 1999, and conflicting national standards shall be withdrawn at the latest by December 1999.

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

For relationship with EU Directive(s), see informative Annex ZA, which is an integral part of this standard.

This European Standard is based on ISO Guide 31 "Contents of certificates of reference materials". The future European Standard "Measurement of quantities in samples of biological origin – Presentation of reference measurement procedures" presents requirements to ensure that values assigned to reference materials by such procedures are reliable and stated in a useful way.

Annexes A, B and ZA are for information only.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

Introduction

To produce useful and reliable results of measurement, whether in science, technology, or routine service, it is necessary that they are supported by a reference measurement system so as to be comparable and ultimately traceable to measurement standards of the highest metrological level.

The substances which are used to obtain this traceability, both through time, distances, and different measurement procedures, are the reference materials. A given reference material is supported by documentation containing descriptions, measurement results, instructions for use, stability data, and storage conditions. The present European Standard specifies the content and format of such supporting documentation.

Reference materials are used for one of three main purposes:

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

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

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

The maximum acceptable uncertainty of measurement of the assigned value of the reference material depends on the requirements of the results of the measurement procedure.

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 (written) standards available are listed in ISO/IEC Guide 15.

1 Scope

This European Standard specifies requirements and formats for the description of reference materials. It is applicable to reference materials of higher metrological order, classifiable as primary measurement standards and secondary measurement standards that function either as calibrators or control materials for reference measurement procedures. This standard does not apply to reference materials that are parts of an in vitro diagnostic measuring system.

This European Standard also provides instructions on how to collect basic data for value determination and how to present the assigned value. The standard also specifies the format for a certificate.

This European Standard is not applicable to the production of the reference materials.

2 Normative references

This European Standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publications referred to applies.

EN 375 : 1992, *In vitro diagnostic systems – Requirements for labelling of in vitro diagnostic reagents for professional use.*

ISO 31 : 1992, *Quantities and units.*

3 Terms and definitions

For the purposes of this Standard, the terms and definitions given in International Vocabulary of Basic and General Terms in Metrology apply (3.1 and 3.2 are quotes from VIM) together with the following:

3.1
primary measurement standard
standard that is designated or widely acknowledged as having the highest metrological qualities and whose value is accepted without reference to other standards of the same quantity [6.4 of VIM]

NOTE 1: The concept of primary standard is equally valid for base quantities and derived quantities.

NOTE 2: The word "measurement" has been included in the term here for consistency.

NOTE 3: Measurement standards include reference materials.

3.2
secondary measurement standard
standard whose value is assigned by comparison with a primary standard of the same quantity [6.5 of VIM]

NOTE 1: The word "measurement" has been included in the term here for consistency.

NOTE 2: Measurement standards include reference materials.

3.3
matrix (of a material system)
all components of a material system except the analyte

3.4
matrix effect
influence of a property of the sample, independent of the presence of the analyte, on the measurement and thereby on the value of the measurable quantity

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 may be influenced by the viscosity of the sample.

3.5
commutability of a material
ability of a material to yield the same numerical relationships between results of measurements by a given set of measurement procedures, purporting to measure the same quantity, as those between the expectations of the relationships obtained when the same procedures are applied to other relevant types of material

NOTE: For reference materials used to calibrate measurement procedures intended for biological samples, "other relevant types of material" include a large number of samples from healthy and relevantly diseased individuals.

3.6
report
document giving detailed information on a reference material, supplementary to that contained in a certificate or package insert

NOTE: The information may comprise the preparation of the reference material, methods of measurement, factors affecting trueness, statistical treatment of results, and the way in which traceability was established.

4 Classification and naming of reference materials

4.1 Description of the properties of reference materials

A reference material has properties, each of which shall be described according to the following format:

a) system (i. e. the material itself);

b) any relevant component(s); and

c) kind-of-quantity (quantity in a general sense).

If the property is a measurable quantity, it shall have a value that is equal to

d) a numerical value multiplied by

e) a unit of measurement.

EXAMPLE:
Certified reference material(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

4.2 System

4.2.1 Function

The reference material shall be capable of functioning as one of the following:

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 analytical trueness or uncertainty of measurement 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 reference material shall perform only one of the functions, and which one shall be specified by the term calibration material (calibrator) or control material.

4.2.2 Application and authorities

The application and authorities of the system shall consist of the following:

a) geographical scope; e. g. international, regional, national, local;

b) responsible body, e. g. authority, institution, company, or laboratory;

c) certification of properties where applicable.

NOTE: Examples of the responsible bodies of item b) include the World Health Organization (WHO), the Standards, Measurements and Testing Programme of the European Commission, national reference institution, manufacturer of separately available reference materials or a specialized hospital laboratory. In item c) some values may have to be certified, e. g. by the Standards, Measurements and Testing Programme of the European Commission or by the National Institute of Standards and Technology (NIST) of USA. Other values may be given for information only.

4.2.3 Hierarchical position of reference materials of higher order in the reference measurement system

Measurement standards of higher order shall be classified according to their positions in the reference measurement system for a given quantity as follows:

a) primary measurement standard (see 3.1);

b) secondary measurement standard (see 3.2).

4.2.4 Identification code(s)

An identification code shall be assigned to the reference material. A lot identification shall be included when available.

4.2.5 Reference material characteristics

The characteristics of the reference material shall be described in the following terms:

a) The origin and nature of the starting material: inorganic, organic, synthetic, natural, or biological of a stated species, e. g. human, porcine.

b) The matrix:

– simple, when a reference material consists of a pure component in a well-defined medium;

– complex, when the component is present in a partially known milieu, e. g. stabilized blood or serum.

c) The physical state of the analyte in the material: solution, colloid, or suspension.

d) The physical state of the reference material: solid, liquid, or gas.

e) Homogeneity and phases: a description of the reference material in terms of one or more individual homogeneous or inhomogeneous phases, e. g. blood can be considered a combination of a homogeneous plasma phase and an inhomogeneous cell phase.

4.3 Component(s)

The component(s) 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, for enzymes the EC number.

EXAMPLES:
Aliphatic carboxylate (C_{10} to C_{26}, non-esterified), fibrinogen (340 000), iron (II+III), and lactate dehydrogenase (E.C.1.1.1.27) isoenzyme 1, basic fibroblast growth factor (human, rec. DNA).

4.4 Kind-of-quantity (quantity in a general sense)

The kind-of-quantity (quantity in a general sense), e. g. mass, amount-of-substance, number fraction, 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 1: "Quantity in a general sense" is the VIM term for what IFCC/IUPAC has called kind-of-quantity.

NOTE 2: Appropriate names and symbols for kind-of-quantities (quantities in the general sense) are given in ISO 31 and in publications by IFCC and IUPAC.

4.5 Numerical value

The number of significant figures of the result shall be chosen so that the uncertainty of measurement 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 they should be separated by a space in groups of three counting from the mark to the left or right.

4.6 Unit of measurement

The unit chosen shall be an SI unit or other legal unit whenever possible.

NOTE: WHO defines some off-system units called International Units.

4.7 Construction of systematic designations and trivial names

A systematic name and value shall consist of elements as specified in 4.2 to 4.6 and shall be given in the format as specified in 4.1.

EXAMPLE 1:
Primary reference material for calibration/control(WHO IS XXX; certified; lyophilized)--Component; kind-of-quantity = (xxx ± xx) unit; average and expanded uncertainty giving an interval estimated to have a level of confidence of 0,95.

EXAMPLE 2:
A systematic name of a calibrator for a haematology analyser can be

Secondary reference material for calibration (Responsible body NN; Product no YYYY)--

Erythrocytes; number concentration = (xxx ± vv) unit; average and expanded uncertainty (level of confidence of 0,95)

Leukocytes; number concentration = (vvv ± zz) unit; average and expanded uncertainty (level of confidence of 0,95)

Thrombocytes; number concentration = (zzz ± yy) unit; average and expanded uncertainty (level of confidence of 0,95).

4.8 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 reference material in the measurement.

EXAMPLE 1:
The trivial name for the material given in Example 1 of 4.7 can be WHO(IS XXX)--Component.

EXAMPLE 2:
The trivial name in general form for the material given in Example 2 of 4.7 can be

Calibrator(Responsible body NN; Product no YYYY)--Erythrocytes, Leukocytes and Thrombocytes;

or even

Calibrator(Responsible body NN; Product no YYYY)--Blood cells.

The trivial name for the corresponding individual product can be

Calibrator(Company NN; Product no YYYY; Batch no AAAA)--Blood cells.

5 Description of a reference material

5.1 Elements of a description

The description of a reference material of higher metrological order shall comprise at least the elements listed as mandatory (M) in Table 1.

NOTE: The order of the elements listed in Table 1 may be changed and additional elements, such as an abstract, may be added as appropriate.

Table 1: Main elements (clauses) of a report describing a reference material of higher metrological order

Element	Type [1])		Subclause in this European Standard
	M	O	
Title page	I		
Contents list		I	
Foreword	I		
Warning and safety precautions	N		5.2
Introduction		I	5.3
Title of report	N		
Scope	N		5.4
Definitions		N	
Symbols and abbreviations		N	
Terminology		N	5.5
Justification for choice of reference material	I		5.6
General characteristics	I		5.7
Specific characteristics	I		5.8
Validation	I		5.9
Intended function	I		5.10
Instructions for use	I		5.11
Supplier	I		5.12
Bibliography		I	5.13
Annexes		I	5.14
Dates	I		5.15

[1]) Symbols for type of element in a European Standard:
M mandatory, O optional;
I informative, N normative.

5.2 Warning and safety precautions

5.2.1 Attention shall be drawn to any danger associated with the reference material and its use. All necessary precautions shall be described. Regional, national, and local legislation and regulations may apply.

5.2.2 This information shall be printed in capital letters or in bold type as follows:

a) immediately after the title of the standard if the danger encountered is due to the reference material, 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.

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

5.3 Introduction

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

a) names of measurable quantities in the measurement of which the reference material is intended to be used, indicated by system, component, and kind-of-quantity (quantity in a general sense);

b) systematic description of the reference material according to clause 4;

c) main reasons for the selection of the particular base material for the reference material and for the chosen method of stabilization (e. g. bovine haemolysate stabilized by freezing);

d) reference measurement procedure(s) or other measurement procedure(s) used for assigning values to the reference material;

e) statement that the requirements of a reference material have been met:

– traceability to measurement procedures or reference materials of higher metrological order (when such exist);

– organization of any collaborative studies and the summary results obtained from material-certification studies;

– number of laboratories participating in any such studies;

– number fraction of results collected during the study that were rejected according to stated rules.

5.4 Scope

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 methods of measurement or measurement procedures for which the reference material is produced;

b) methods of measurement or measurement procedures for which the material is known to be unsuitable;

c) influence quantities in the reference material involving, e. g. drugs, metabolites, additives, microbial growth;

d) mentioning of major required pretreatment of the reference material which is not performed on the biological samples according to a specified measurement procedure (for example, reconstitution of lyophilized material).

5.5 Terminology

5.5.1 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 "Definitions" (see table 1) and sometimes also to the clause "Symbols and abbreviations" (see table 1), and the terms may be incorporated in either or distributed between both.