SLOVENSKI STANDARD
SIST EN ISO 17511:2003

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Diagnostiļ ni medicinski pripomoļ ki in vitro - Merjenje koliļ in v vzorcih biologkega izvora ï Meroslovna sledljivost vrednosti, dodeljenih kalibratorjem in kontrolnim materialom (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 17511:2003)

In-vitro-Diagnostika - Messung von Größen in Proben biologischen Ursprungs - Metrologische Rückführbarkeit von Werten, die Kalibriermaterialien und Kontrollmaterialien zugeordnet sind (ISO 17511:2003)

Dispositifs médicaux de diagnostic in vitro - Mesurage des grandeurs dans des échantillons d'origine biologique - Traçabilité métrologique des valeurs attribuées aux agents d'étalonnage et aux matériaux de contrôle (ISO 17511:2003)

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11.100.10	Diagnostiļ ni preskusni sistemi in vitro	In vitro diagnostic test systems

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This European Standard was approved by CEN on 11 March 2003.

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This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the Management Centre has the same status as the official versions.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
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Contents

Foreword

This document (EN ISO 17511:2003) has been prepared by Technical Committee CEN/TC 140 "In vitro diagnostic medical devices", the secretariat of which is held by DIN, in collaboration with Technical Committee ISO/TC 212 "Clinical laboratory testing and in vitro diagnostic test systems".

This European Standard EN ISO 17511:2003 including the Amendment shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by February 2004, and conflicting national standards shall be withdrawn at the latest by February 2004.

This document 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 document.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the European Confederation of Laboratory Medicine (ECLM), and the European Diagnostic Manufacturers Association (EDMA) have contributed to its preparation.

This standard includes a Bibliography.

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, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland and the United Kingdom.

Introduction

For measurements of quantities in laboratory medicine, it is essential that the quantity is adequately defined and that the results reported to the physicians or other health care personel and patients are adequately accurate (true and precise) to allow correct medical interpretation and comparability over time and space.

NOTE In this European Standard the concept "accuracy of measurement" (see 3.1) is related to both "trueness of measurement" (see 3.33) and "precision of measurement" (see 3.23) whereas the Directive 98/79/EC on in vitro diagnostic medical devices uses the term ''accuracy'' instead of ''trueness''.

To allow 'correct medical interpretation' involves more than the metrological (analytical) aspects of the traceability chain. As the measurement results are eventually used by the physician for the benefit of the patients, the physician should gather information on a number of other aspects, such as knowledge about the pre- and post-analytical phase, the diagnostic sensitivity and specificity, and relevant reference interval(s). The present European Standard deals only with the analytical aspects of measurements in Laboratory Medicine (see also 1 e)).

The measurement of quantities in biological samples requires reference measurement systems including:

- the definition of the analyte in the biological sample with regard to the intended clinical use of the measurement results;
- a reference measurement procedure for the selected quantity in human samples;
- suitable reference materials for the selected quantity, e.g. primary calibrators and secondary matrix-based calibrators that are commutable.

The trueness of measurement of a value assigned to a defined quantity of a calibrator or trueness control material, depends on the metrological traceability of the value through an unbroken chain of alternating measurement procedures and measurement standards (calibrators), usually having successively decreasing uncertainties of measurement (see Figure 1). The uncertainty of the value assigned to a given calibrator or trueness control material depends on the stated metrological traceability chain and the combined uncertainties of its links.

The ideal end-point of a metrological traceability chain is the definition of the relevant unit of the International System of Units (SI), but the selection of steps and the level at which metrological traceability for a given value stops, depend on the availability of higher order measurement procedures and calibrators. In many cases, at present, there is no metrological traceability above the manufacturer's selected measurement procedure or the manufacturer's working calibrator. In such cases, trueness is referred to that level of the calibration hierarchy until an internationally agreed reference measurement procedure and/or calibrator becomes available.

The objective of a chosen metrologically traceable calibration is to transfer the degree of trueness of a reference material, and/or reference measurement procedure, to a procedure that is of a lower metrological order, e.g. a routine procedure. Metrological traceability of calibration requires that the reference and routine measurement procedures measure the same measurable quantity with an analyte of the same pertinent characteristics.

In this context, it is important to recognize that different procedures purporting to measure the same quantity may in fact give different results when applied to a particular sample or reference material. This may arise, for example, when two or more immunoprocedures purporting to measure the concentration of a hormone such as thyrotropin (thyroid stimulating hormone, TSH) are applied to a reference material of the hormone, because the respective reagents recognize and react to different extents with various epitopes in the material, thus leading to results for different although related quantities.

Laboratory medicine routinely provides results for 400 to 700 types of quantity. For most of these, the metrological traceability of the assigned value for a product calibrator stops after only one metrologically higher step consisting of a (reference) measurement procedure, or after two steps consisting of a measurement procedure and a (reference) calibrator. The reason is that many of such quantities are related to mixtures of molecular species with clinically relevant properties in common, but with different structures and molecular masses in varying proportions, e.g. glycoproteins.

Depending on the possibility of metrological traceability to SI and on the availability of various metrological levels of measurement procedures and calibrators, the following five typical upper ends of the metrological traceability chain can be identified.

a) Quantities for which results of measurements are metrologically traceable to SI.

A primary reference measurement procedure and one or more (certified) primary reference materials (used as calibrators) are available. These levels exist for approximately 25 to 30 types of quantity having well defined components, e.g. some electrolytes, metabolites, steroid hormones, and some thyroid hormones. These types of quantity cover a large proportion of the routine results provided by medical laboratories (see 4.2.2, 5.2, Figures 1 and 2).

b) Quantities for which results of measurements are not metrologically traceable to SI.

1) An international conventional reference measurement procedure (see 3.12) (which cannot be called a primary reference measurement procedure) and one or more international conventional calibration materials (see 3.11) with values assigned by that procedure are available. These conditions apply for quantities with components such as HbA_{1c} (see 5.3 and Figure 3).

2) An international conventional reference measurement procedure is available but no international conventional calibration materials. These conditions apply for about 30 types of quantity with components such as haemostatic factors (see 5.4 and Figure 4).

3) One or more international conventional calibration materials (used as calibrators) with a protocol for value assignment are available, but no international conventional reference measurement procedure. These conditions apply for over 300 types of quantity, e.g., for quantities referred to World Health Organization's International Standards, such as protein hormones, some antibodies, and tumour markers (see 5.5 and Figure 5).

4) Neither reference measurement procedure nor reference materials for calibration are available. The manufacturer can establish 'in-house' measurement procedure(s) and calibrator(s) to support value assignment to his product calibrator. These conditions apply for about 300 types of quantity with components such as tumour markers and antibodies (see 5.6 and Figure 6).

The principles of the respective transfer protocols (calibration hierarchies) are presented, given the provisions of the European Standards EN 12286 on presentation of reference measurement procedures and EN 12287 on the description of reference materials.

It is the aim of metrology in laboratory medicine to improve metrological traceability for results of a type of quantity from the conditions described under b2), b3), and b4) to those of b1) by providing the missing reference measurement procedures and reference materials, based on international consensus.

The special problems of metrological traceability for values of catalytic concentration of enzymes are considered in prEN ISO 18153.

1 Scope

This European Standard specifies how to assure the metrological traceability of values assigned to calibrators and control materials intended to establish or verify trueness of measurement. The calibrators and control materials are those provided by the manufacturers as part of, or to be used together with, in vitro diagnostic medical devices.

External quality assessment (survey) samples, with proven commutability, whose values have been assigned by means of internationally agreed reference measurement systems or internationally agreed conventional reference measurement systems fall within the scope of this European Standard.

This European Standard is not applicable to:

a) control materials that do not have an assigned value and are used only for assessing the precision of a measurement procedure, either its repeatability or reproducibility (precision control materials);

b) control materials intended for intralaboratory quality control purposes and supplied with intervals of suggested acceptable values, each interval obtained by interlaboratory consensus with respect to one specified measurement procedure, and with limiting values that are not metrologically traceable;

c) correlation between results of two measurement procedures at the same metrological level, purporting to measure the same quantity, because such 'horizontal' correlation does not provide metrological traceability;

d) calibration derived from correlation between the results of two measurement procedures at different metrological levels, but with quantities having analytes of different characteristics;

e) metrological traceability of routine results to the product calibrator and their relations to any medical discrimination limit;

f) properties involving nominal scales, i.e. where no magnitude is involved (e.g. identification of blood cells).

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 publication referred to applies (including amendments).

EN 375:2001, *Information supplied by the manufacturer with in vitro diagnostic reagents for professional use.*

International Vocabulary of Basic and General Terms in Metrology, 2nd edition, ISO, Geneva, 1993.[1)2)]

ISO Guide 35:1989, *Certification of reference materials - General and statistical principles.*

3 Terms and definitions

For the purposes of this European Standard, the following terms and definitions apply:

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

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[1)] This monograph 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)

[2)] The abbreviation VIM:1993 is used in this standard

[VIM:1993, 3.5]

NOTE 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 estimator of an inverse measure of accuracy is "deviation", defined as 'value minus a conventional true value'.

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

NOTE 5 In this standard the concept "accuracy of measurement" is related to both "trueness of measurement" (see 3.33) and "precision of measurement" (see 3.23) whereas the Directive 98/79/EC on in vitro diagnostic medical devices uses the term 'accuracy' instead of 'trueness'.

3.2
analyte
component represented in the name of a measurable quantity

EXAMPLE In the type of quantity "mass of protein in 24-hour urine", "protein" is the analyte. In "amount of substance of glucose in plasma", "glucose" is the analyte. In both cases the long phrase represents the measurand (see 3.17).

3.3
analytical specificity
ability of a measurement procedure to measure solely the measurand

3.4
bias of measurements
difference between the expectation of the results of measurement and a true value of the measurand

NOTE An estimator is the "statistical sample bias of measurements" which is the 'average minus its reference value'.

3.5
calibration
set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards

[VIM:1993, 6.11]

NOTE The term "standard" here refers to "measurement standard" (see 3.19), not a written standard.

3.6
calibration transfer protocol
transfer protocol
detailed description for assigning a value of a quantity to a reference material using a specified sequence of measurement procedures calibrated by higher-order reference materials for the same type of quantity

3.7
calibrator
calibration material
reference material whose value is used for the independent variable in a calibration function

3.8
certified reference material
CRM
reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes metrological 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

[slightly adapted from VIM:1993, 6.14]

3.9
commutability of a material
closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material, and the mathematical relationship obtained for the quantity in routine samples

3.10
influence quantity
quantity that is not the measurand but that affects the result of the measurement

[VIM:1993, 2.7]

3.11
international conventional calibrator
international conventional calibration material
calibrator whose value of a quantity is not metrologically traceable to the SI but is assigned by international agreement

NOTE The quantity is defined with respect to the intended clinical application.

3.12
international conventional reference measurement procedure
measurement procedure yielding values that are not metrologically traceable to the SI but which by international agreement are used as reference values for a defined quantity

NOTE The quantity is defined with respect to the intended clinical application.

3.13
international measurement standard
international standard
standard recognized by an international agreement to serve internationally as the basis for assigning values to other standards of the quantity concerned

[VIM:1993, 6.2]

3.14
matrix of a material system
matrix
totality of components of a material system except the analyte

[EN 12287:1999, 3.3]

3.15
matrix effect
influence of a property of the sample, other than the measurand, on the measurement of the measurand according to a specified measurement procedure and thereby on its measured value

NOTE 1 A specified cause of a matrix effect is an influence quantity.

NOTE 2 The term 'matrix effect' is sometimes erroneously used for the lack of commutability due to a denatured analyte or an added non-genuine component ('surrogate analyte') meant to simulate the analyte.

3.16
measurable quantity
quantity
attribute of a phenomenon, body or substance that may be distinguished qualitatively and determined quantitatively

[VIM:1993, 1.1]

NOTE 1 Properties that are expressed on a nominal scale are not measurable quantities.

NOTE 2 "Measurable quantity" is not to be confused with "analyte", see 3.2.

3.17
measurand
particular quantity subject to measurement

[VIM:1993, 2.6]

NOTE See 3.2, Example.

3.18
measurement procedure
set of operations, described specifically, used in the performance of particular measurements according to a given method

[VIM:1993, 2.5]

3.19
measurement standard
material measure, measuring instrument, reference material or measuring system intended to define, realize, conserve or reproduce a unit or one or more values of a quantity to serve as a reference

[VIM:1993, 6.1]

NOTE 1 A given measurement standard with an assigned value for one quantity can sometimes serve as a reference material for measurement procedures yielding values for more than one type of quantity. (For example, a reference material for cholesterol also serving for cholesterol esters that are measured after hydrolysis as cholesterol).

NOTE 2 The term 'standard' is used with two meanings: "measurement standard" and "written standard". The full terms should be used when doubt can arise.

3.20
method of measurement
logical sequence of operations, described generically, used in the performance of measurements

[VIM:1993, 2.4]

NOTE A method of measurement, due to its generalized description, does not have numerically specified performance characteristics. A given method can be the basis of one or more measurement procedures, each with inherent numerical values for its performance characteristics.

3.21
metrological 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]

NOTE 1 Each comparison is effected by a (reference) measurement procedure defined in a calibration transfer protocol.

NOTE 2 There are several types of traceability. Therefore the term 'metrological traceability' is used in the present text.

3.22
metrology
science of measurement

NOTE Metrology includes all aspects both theoretical and practical with reference to measurements, whatever their uncertainty, and in whatever fields of science or technology they occur.

[VIM:1993, 2.2]

3.23
precision of measurement
closeness of agreement between independent results of measurements obtained under stipulated conditions

[ISO 3534-1:1993, 3.14]

NOTE 1 Precision of measurement cannot be given a numerical value in terms of the measurand, only descriptions such as 'sufficient' or 'insufficient' for a stated purpose.

NOTE 2 The degree of precision is usually expressed numerically by the statistical measures of imprecision of measurements, such as standard deviation and coefficient of variation, that are inversely related to precision.

NOTE 3 "Precision" of a given measurement procedure is subdivided according to the specified precision conditions. "Repeatability" relates to essentially unchanged conditions and is often termed "withinserial" or "within-run precision". "Reproducibility" relates to changes in conditions, e.g. time, different laboratories, operators, and measuring systems (including different calibrations and reagent batches).

3.24
primary reference material
reference material having the highest metrological qualities and whose value is determined by means of a primary reference measurement procedure

NOTE 1 The concept "primary calibrator" is subordinate to "calibrator" (see 3.7) and to "primary reference material".

NOTE 2 See 3.26, Note.

3.25
primary reference measurement procedure
reference measurement procedure 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 where results are, therefore, accepted without reference to a measurement standard of the quantity being measured

NOTE The Consultative Committee on Amount of Substance (CCQM) uses the term "primary method of measurement", but the term "primary reference measurement procedure" in the present context is in conformity with VIM (see 3.19 with Note). The term "definitive method"' was omitted in VIM, but is sometimes used for a thoroughly investigated and evaluated reference measurement procedure (see 3.29) of high accuracy.

3.26
primary measurement standard
primary 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

[VIM:1993, 6.4]

NOTE For reference materials, the value can be obtained by applying a primary reference measurement procedure.

3.27
product calibrator
calibrator intended for use with the manufacturer's final product

3.28
reference material
RM
material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement procedure, or for assigning values to materials

NOTE 1 Adapted from VIM:1993, 6.13.

NOTE 2 The adjective 'homogeneous' refers to the physical homogeneity between macroscopic parts of the material, not to any microheterogeneity between molecules of the analyte.