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

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

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 15193 was prepared by the European Committee for Standardization (CEN) Technical Committee CEN/TC 140, In vitro *diagnostic medical devices*, in collaboration with Technical Committee ISO/TC 212, *Clinical laboratory testing and* in vitro *diagnostic test systems*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO 15193:2002), which has been technically revised.

Introduction

Reference measurement systems are needed to produce useful and reliable measurement results, whether in science, technology or routine service, so as to be comparable and ultimately metrologically traceable to measurement units and/or measurement standards and/or measurement procedures of the highest metrological level. Reference measurement procedures play a crucial role in this metrological system because they can be used for the following:

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

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

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

d) in detecting analytical influence quantities in patient samples.

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

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

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

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

The advantages of having such a standard are listed in ISO/IEC Guide 15.

In Clause 3 of this International Standard, concepts are indicated by *italicized text*.

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

1 Scope

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

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

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

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

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

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

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

ISO/IEC Guide 98-3:2008, *Guide to the expression of uncertainty in measurement (GUM:1995)*

ISO/IEC Guide 99:2007, *International vocabulary of metrology — Basic and general concepts and associated terms (VIM)*

3 Terms and definitions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.11
influence quantity
quantity that, in a direct measurement, does not affect a quantity that is actually measured, but affects the relation between the indication and the measurement result

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

3.12
measurand
quantity intended to be measured

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

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

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

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

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

NOTE 2 The abbreviation LOD is sometimes used.

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

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

3.14
calibrator
measurement standard used in calibration

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

4 Presentation of a reference measurement procedure

4.1 Elements of a reference measurement procedure

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

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

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

4.2 Warning and safety precautions

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

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

4.3 Introduction

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

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

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

c) measurement method and rationale for its choice;

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

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

f) metrological traceability.

4.4 Scope

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

The scope should include the following items:

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

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

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

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

e) measurement interval.

4.5 Terms, definitions, symbols and abbreviated terms

4.5.1 Concepts

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

NOTE These can include, for example:

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

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

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

4.5.2 Nomenclature

The names of chemical compounds, biological components, quantities, units and symbols used shall be in accordance with available International Standards (or European Standards if appropriate), or the latest recommendations of the appropriate international organization(s). When more than one name is recommended by authoritative sources, a single name may be chosen. The chosen name and synonyms shall be listed with reference to the relevant standard or recommending organization.

4.5.3 Trivial names

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

4.6 Measurement principle and measurement method

4.6.1 The measurement principle shall be given, e.g. molecular absorption of visible light applied in a procedure for measuring the amount-of-substance concentration of bilirubins in a liquid solution.

4.6.2 The measurement method shall be described. If appropriate, the reasons for the choice of a certain step shall be given. Essential chemical reactions shall be indicated if they help in understanding the text or the calculations. The reactions shall, if appropriate, be expressed in ionic form.

4.7 Check list

4.7.1 Appropriateness

If included, the checklist shall list the items and conditions that are required to perform the measurements.

NOTE A checklist is especially useful if the document is large. It is particularly applicable to reagents (see 4.8) and to apparatus (see 4.9). The full descriptions and instructions for preparation of reagents would be given later in the text or as an annex.

4.7.2 List of reagents and materials

If reagents are incorporated in the checklist, they shall be listed by systematic or trivial name.

This clause should be drawn up in the following systematic order:

a) products (excluding solutions) used in their commercially available form;

b) solutions, suspensions, or powders (excluding reference materials) with their approximate concentrations stated;

c) calibration materials such as solutions with defined concentrations;

d) indicators;

e) solvents (water, organic solvents);

f) control materials.

4.7.3 List of pieces of apparatus

The main pieces of apparatus shall be listed, together with their type and any particular requirements, such as officially calibrated instruments (e.g. balances and volumetric devices).

4.7.4 List of pieces of auxiliary equipment

Other pieces of apparatus, not listed in accordance with 4.7.3, shall be listed, together with their type and other appropriate information, such as material, grade, calibration, size and any other particular performance requirements.

4.7.5 List of special laboratory requirements

Any physical, environmental and safety requirements necessary to the measurement shall be fully defined.

4.8 Reagents and materials

4.8.1 General

Unless otherwise stated, only reagents and solvents of appropriate documented analytical properties shall be used.

When a reagent or preparation requires further definition, description of the material, manufacturer or vendor, and in some cases the lot number, is helpful.

If a reagent is specified as to brand name, a note should be added that other brands may be substituted if requirements are met.

4.8.2 Descriptive items

The following information shall be given as appropriate for each commercial and in-house reagent in monographical form:

a) Chemical Abstract Service Registry Number (CAS-, CARN-number);

b) trivial name [main component(s) and/or property/properties)];

c) as far as possible, full systematic chemical or, for each property of the prepared reagent in the final form, biological name for labelling with component name, associated kind-of-property name and value of property, possibly with a defined measure of measurement uncertainty, in accordance with ISO 15194;

d) production details for in-house reagents, stating as necessary:

   1) for each starting material used

      — if a chemical, the chemical formula (including water of crystallization), molar mass, analytical properties (e.g. purity, specified impurities);

      — if a biological material, its type and origin;

   2) acceptable performance commensurate with its use;

   3) checking procedure along with tolerance intervals, e.g. for absence of interfering components;

   4) utensils and special cleaning procedures;

e) storage conditions;

f) shelf life;

g) disposal;

h) hazard class with symbol, R-phrases, and S-phrases (see References [26] and [27]).

If general methods for the preparation and checking of certain utilized reagents are the subject of International Standards, a reference to such International Standards shall be made (see 4.8.1).

4.8.3 Influence quantities

If critical to the measurement, all influence quantities shall be specified, e.g. temperature for volume measurements.

4.8.4 Expression of concentration

For solutions with accurately defined concentration for titrimetry, the concentration shall be expressed as amount-of-substance concentration (with indication of the elementary entity) in mole per cubic metre (mol/m^3) or mole per litre (mol/l).

In certain cases, e.g. when the elementary entity is not known, mass concentration may be given with the unit, e.g. gram per litre (g/l).

Units such as ppm (parts per million; equal to 10^{-6}) and ppb (parts per billion; equal to 10^{-9}) shall not be used.

The kind-of-quantity terms “normality” and “molarity” shall be abandoned in favour of the designation “amount-of-substance concentration”, with the elementary entity of the component (analyte) indicated if necessary. Designations such as “substance concentration” or “amount concentration” should be avoided.

If the composition of a reagent solution cannot be given as amount-of-substance concentration, some other expression shall be chosen, e.g.

a) mass concentration [unit kilogram per litre (kg/l) or appropriate numerator submultiples thereof],

b) mass fraction [unit one (1) or kilogram per kilogram (kg/kg)],

c) volume fraction [unit one (1) or litre per litre (l/l)], and

d) catalytic-activity concentration, catalytic concentration [unit mole per litre second ($mol/l^{-1}s^{-1}$) equal to katal per litre (kat/l)].

NOTE The unit U/ml (enzyme unit per millilitre) is equal to $16{,}67 \times 10^{-6}$ kat/l.

The measured catalytic-activity concentration value depends on the measurement procedure, which shall be specified.

4.8.5 Diluting

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.

4.8.6 Reference to patented items

If, in exceptional cases, technical reasons justify the preparation of a reference measurement procedure 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 reference measurement procedure involves the use of a patent.

NOTE For a reference measurement procedure intended as an International Standard, see ISO/IEC Directives, Part 1, 2008, 2.14, and ISO/IEC Directives, Part 2, 2004, Annex F.

4.9 Apparatus

4.9.1 Description

Each item of apparatus shall be described by:

a) name (generic) and, if necessary, type, manufacturer, model number, instrument serial number, or batch codes, and

b) essential performance properties.

4.9.2 Auxiliary equipment

Auxiliary equipment shall be described in a separate subclause analogously to 4.9.1, as appropriate.

4.10 Sampling and sample

4.10.1 General

If the measurement results are known to be influenced by preanalytical factors that change some properties of the primary sample, such factors shall be listed together with any means of identification or precautions.

NOTE The factors include genetic factors, gender, pregnancy, environmental factors, diet, drugs, physiological exercise, timing, posture, stasis before venous blood sampling, preparatory treatment of the sampling site and handling of primary sample.

4.10.2 Samples

Requirements for the primary sample shall be specified in terms of required sample container and/or sample handling procedure, as required to minimize changes of the measurand (e.g. loss and/or contamination), acceptable material, amount required, additives required, transport conditions, storage conditions, stability, hazards and precautions.

Requirements for the laboratory sample shall be specified with respect to how to obtain it, type and amount of acceptable material, storage conditions, any thawing procedure and mixing.

The steps in the preparation of the analytical sample shall be described, e.g. separation, grinding, mixing, freeze drying, storage and reconstitution.

4.11 Preparation of measuring system and analytical portion

4.11.1 General

The analytical steps in the preparation of the measuring system and analytical portion can be presented in the form of a table or flow diagram or other schematic representation, in order to facilitate understanding and to provide overview.

4.11.2 Preparation of apparatus

The preparation of apparatus prior to carrying out the measurement shall be defined and described if different from the procedure given in the manufacturer's instructions for use, including the following, as appropriate:

a) warnings and safety precautions;

b) assembly;

c) checking that the tolerance limits of performance quantities are not exceeded;

d) operating mode;

e) user's preventive maintenance.

4.11.3 Calibration

The principle, materials and steps involved in any calibration shall be described in detail in terms of the following:

a) choice of type of calibration procedure [number of calibrator values, e.g. two-point, multiple point; bracketing (see 4.11.5); standard addition] and quality requirements;

b) suitable calibrators and any checks of their required specifications, e.g. metrological traceability in accordance with ISO 17511 or ISO 18153;

c) calibrator preparation(s), e.g. gravimetric and volumetric preparation of dilutions or standard addition technique;

d) measurement of calibrator(s);

e) method of computing a monotonic (continuously increasing or decreasing) calibration function and the measurement uncertainties of its parameters;

f) acceptance of calibration function according to established criteria; and

g) time interval of recalibration within series (also called runs) and/or between series.

4.11.4 Types of analytical sample

The different types of allowed analytical sample shall be listed and described.

NOTE They can derive from primary sample, calibrator material or control material, including matrix material.

4.11.5 Structure of analytical series

When a serial arrangement of material from the analytical samples is used, the series (or run) shall be specified as to sequence and numbers of:

a) calibrator(s) (if applicable),

b) control material(s) (if applicable),

c) blank material(s) (if applicable), and

d) "unknown" material(s) to be analysed.

NOTE The bracketing principle of using calibrator with a lower value, unknown material, calibrator with a higher value in repeated runs is a powerful way of reducing the measurement uncertainty of measurement results.

The precautions against carry-over of material from one sample to the next shall be presented and maximum values set.

4.11.6 Analytical portion

The description of the analytical portion shall state, as appropriate, any hazards as well as precautions, procedures and accuracy required for measuring amount(s), and the steps in any pre-treatment.

4.11.7 Analytical solution

The preparation of any analytical solution shall be described.

4.12 Operation of measuring system

4.12.1 Sequence of measurement steps

Each step of the measurement shall be described unambiguously (see ISO 78-2). The sequence shall be set out clearly in subclauses and paragraphs.

The sequence of measurement steps shall include the following items, as appropriate:

a) verification of the performance of the measuring functions of equipment, including those of auxiliary equipment;

b) measurement on the analytical portion described stepwise;

c) indication of the measuring system.

4.12.2 Blanking

The preparation of blank analytical portions of analytical sample blank and analytical reagent blank shall be detailed where applicable.

4.12.3 Validation of initial data

When the initial data are obtained, they shall be validated. Guidelines shall be given on how the operator may ensure that the equipment functions properly and that ambient conditions are satisfactory, and how values measured on calibrators, samples and blanks, as appropriate, shall lie within stipulated intervals. This initial validation shall be in accordance with the requirements as specified in 4.13.1, 4.14 and 4.18 respectively.

4.12.4 Stand-by and closing-down procedures

If essential for the measurement, instructions shall be given for setting the equipment in a stand-by mode and for closing it down.

4.12.5 Schematic representation of procedure

A table or flow diagram or other schematic representation of the use of the measuring system may facilitate understanding and overview.

4.13 Data processing

4.13.1 Calculation of measurement results

The procedure to calculate the measurement results shall include the following:

a) processing of initial data (see 4.12.3), including blank corrections, repeated values;

b) construction of measuring function;

NOTE The measuring function is usually the inverse of the calibration function.

c) the kind-of-quantity and measurement unit in which the measurement result shall be expressed;

d) the model for statistical treatment of measured quantity values;

e) the complete equation used for calculation of a measurement result, using only quantity symbols, mathematical signs and numbers; the symbols shall be explained in a list, also stating the measurement units in which symbols are expressed; the meaning of any numerical factors shall be explained;

f) the description of any algorithm used;

g) the minimum number of points to generate the measuring function;

h) the number of replicate measured quantity values necessary to calculate a measurement result, their allowable maximum difference and the equation used;

i) the number of significant figures in the measurement result and any rounding procedure (see also ISO Guide 33); and

j) calculation of measurement uncertainty.

Recommendations on data storage, if necessary, may be given in a separate clause.

4.13.2 Conversion equations

The equations used in converting between the recommended expression of measurement results and results expressed in other kinds-of-quantity and/or measurement units shall be given.

EXAMPLE An equation converting amount-of-substance concentration of haemoglobin(Fe) in blood plasma into mass concentration.

4.13.3 Comparison with measurement results obtained by other measurement procedures

If relevant for comparability, comparative data shall be given on measurement results on various types of sample to which the reference measurement procedure is claimed to apply with the procedure presented and with alternative measurement procedures differing in measurement principle, measurement method or details of measurement procedure.

4.14 Analytical reliability

4.14.1 Concepts, values and their use

The values and their respective measurement uncertainties shall be stated for all analytical performance properties.

NOTE The analytical reliability of a measurement procedure can only be estimated by several analytical performance properties. These are essential in assessing the suitability of a measurement procedure for a given task.

4.14.2 Analytical calibration function

The analytical calibration function shall be given.

NOTE This fundamental function, which can be presented as a calibration curve (or analytical curve), is the indication (or output signal) of the measuring system (Y axis) against the stimulus (or input signal) from materials with reference quantity values under consideration (X axis).

4.14.3 Analytical sensitivity

The analytical sensitivity shall be given.

This quantity is the slope of the calibration curve (or analytical curve). If the calibration function is neither linear nor transformable to a linear relationship, the slope at various quantity values should be given.

NOTE The term “analytical sensitivity” is not a synonym for “detection limit” (see 4.14.14), although it is often so defined.

4.14.4 Analytical measuring function

The analytical measuring function shall be used when converting an indication into a measured quantity value. The method of calculating the measuring function and its uncertainty measures at various levels shall be given.

4.14.5 Linearity or other form of analytical measuring curve

When appropriate, the linear portion of the measuring curve shall be stated as an interval of quantity values. In other cases, an interval shall be given within which another known mathematical function applies.

4.14.6 Analytical influence quantities

Information shall be given on the effect of analytical influence quantities that have been checked. Their respective effects in terms of quantity value at relevant levels of influence quantities and relevant levels of measurand shall be stated.

EXAMPLE 1 The increase in measured concentration of bilirubin in human serum as a consequence of admixture of haemoglobin is an example of an influence quantity.

EXAMPLE 2 Phosphate can interfere with the signal from calcium in atomic absorption spectrometry.

4.14.7 Blank measurement

If appropriate, the adequacy of blank measurements (see 4.12.2) in correcting for background effects shall be indicated.

4.14.8 Recovery measurement

Where relevant, recovery measurements shall be made and the results stated.

4.14.9 Measurement uncertainty

The estimate of each systematic effect of known cause shall be used with an opposite sign as a correction added or be expressed as a correction factor or a more complex function. Measurement uncertainties arising from the unavoidably imperfect corrections for systematic effects shall be incorporated in the uncertainty budget (see also ISO/IEC Guide 98-3). It shall be an objective in designing a reference measurement procedure to eliminate all known causes of systematic effect.

A set of measured quantity values will show a dispersion due to random effects and the measurement uncertainty shall be characterized by statistics for which limits can be given (see 4.14.12 and 4.14.13). An estimate of measurement uncertainty shall be linked to defined precision conditions.

The measurement uncertainty is inherent to the measurement procedure and shall be distinguished from effects of mistake.

4.14.10 Measurement accuracy

As measurement accuracy is a “qualitative” concept, a value in the form of a product of a numerical value and a measurement unit cannot be assigned; only subjective scale values such as “poor” and “good” can be used. Therefore, the measurement accuracy, covering measurement trueness and measurement precision, shall be expressed in terms of one or both of the following forms of measurement uncertainty on a rational scale:

a) a combined measurement uncertainty, u_c, obtained as the outcome of an uncertainty budget;

b) an expanded measurement uncertainty, U, with the coverage factor, k, specified as follows:

$$U = k \cdot u_c$$

4.14.11 Measurement precision

Rational-scale measures of the measurement precision are standard deviation, variance and coefficient of variation. Each of these measures shall be specified as follows:

a) repeatability conditions, i.e. the intra-run situation (see 4.14.12);

b) intermediate precision conditions, i.e. a defined between-run situation in a given laboratory;

c) reproducibility conditions where several laboratories are involved (see 4.14.14).

As measurement precision is a “qualitative” concept, a measured quantity value in the form of a product of a numerical value and a measurement unit cannot be assigned; only subjective ordinal-scale values such as “poor” and “good” can be used.

4.14.12 Repeatability standard deviation, s_r

The repeatability standard deviation, s_r, shall be stated [see ISO 5725-2 and 4.14.11 a) in this International Standard], preferably with a measurement uncertainty. If the value varies with the quantity value, a table or function shall be given.

NOTE 1 Synonyms are intra-run standard deviation, intra-series standard deviation, within-run standard deviation and within-series standard deviation.

NOTE 2 Presentation of repeatability statistics are given in ISO 78-2.

4.14.13 Intermediate precision standard deviation

The value of the intermediate precision standard deviation shall be stated [see ISO 5725-3 and 4.14.11 b) in this International Standard], together, if possible, with its measurement uncertainty. If the value varies with the quantity value, a table or function shall be given.

It shall furthermore be made clear which precision conditions are involved in changes and whether the repeatability variation (see 4.14.12) is included or purged.

4.14.14 Reproducibility standard deviation, s_R

The value of the reproducibility standard deviation, s_R, shall be stated [see ISO 5725-2 and 4.14.11 c) in this International Standard], together, if possible, with its measurement uncertainty. If the value varies with the quantity value, a table or function shall be given. It shall furthermore be made clear whether the repeatability variation (see 4.14.12) and intermediate precision variation (see 4.14.13) are included or purged.

NOTE Presentation of reproducibility statistics is given in ISO 78-2 and References [21] and [23].

4.14.15 Detection limit

The detection limit shall be stated.

NOTE The value is influenced by analytical sensitivity (see 4.14.3), measurement accuracy (see 4.14.10), measurement precision (see 4.14.11) and the distribution of blank values (see 4.14.7). It can be calculated with regard to stated probabilities of analytically false negative and false positive measurement results. See ISO 5725-4 and Reference [23].

4.14.16 Lower and higher measurement limits

The lower and higher measurement limits shall be stated.