INTERNATIONAL STANDARD

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

Dispositifs médicaux de diagnostic in vitro — Mesure des grandeurs dans des échantillons d'origine biologique — Présentation des modes opératoires 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 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 15193 was prepared by the European Committee for Standardization (as EN 12286:1998) 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.

The International Federation of Clinical Chemistry and Laboratory Medicine (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 May 1999, and conflicting national standards shall be withdrawn at the latest by May 1999.

This European Standard is based on ISO/DIS 78-2 with special consideration of the requirements for biological materials and for reference measurement procedures. prEN 12287 "In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Description of reference materials" specifies requirements of importance to the calibration and quality assurance of reference measurement procedures.

Annexes A and B 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

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

– in assessing performance characteristics of measuring systems – comprising measuring instruments, auxiliary equipment as well as reagents,

– in demonstrating the functional interchangeability of different routine measurement procedures purporting to measure the same quantity,

– in assigning values to reference materials that are then used for purposes of calibration or control of routine measurement procedures and

– in detecting analytical influence quantities in patient samples.

For clinical laboratory measurements, in particular, it is vitally important to acute and continuous patient care that the results reported to the physicians and patients are adequately comparable, reproducible, and accurate.

In some cases, a reference measurement procedure should be given in the form of a (written) standard, namely when it is related to technical requirements

– specified in standards, technical specifications, or technical regulations, etc.;

– for which values are to be stated by the supplier;

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

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

1 Scope

This European Standard specifies requirements for the drafting of a reference measurement procedure.

NOTE: It is intended that an experienced laboratory worker, following a measurement procedure written in accordance with this European Standard can be expected to produce results with an uncertainty of measurement not exceeding the stipulated range.

This European Standard is applicable to any person, body, or institution, involved in one of the various branches of laboratory medicine, intending to write a document to serve as a reference measurement procedure.

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.

EN ISO 3696 Water for analytical laboratory use – Specification and test methods (ISO 3696 : 1987)

ISO 6353-2 Reagents for chemical analysis – Part 2: Specifications – First series

ISO 6353-3 Reagents for chemical analysis – Part 3: Specifications – Second series

ISO/IEC Directives – Part 2 : 1992 Methodology for the development of International Standards

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

Guide to the Expression of Uncertainty in Measurement, 1st edition, Geneva: ISO, 1993 [1]

3 Definitions

For the purposes of this European Standard, the definitions given in "International Vocabulary of Basic and General Terms in Metrology" and in "Guide to the Expression of Uncertainty in Measurement" apply together with the following:

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 may be taken.

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

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[1]) This document has been prepared 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 is used in this standard.

3.4 analytical portion: Portion of material taken from the analytical sample and on which the measurement or observation is actually carried out.

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

3.5 analytical solution: Solution prepared by dissolving, with or without reaction, an analytical portion in a gas, liquid, or solid.

3.6 matrix (of a material system): All components of a material system, except the analyte.

3.7 reference measurement procedure: Thoroughly investigated measurement procedure shown to yield values having an uncertainty of measurement commensurate with its intended use, especially in assessing the trueness of other measurement procedures for the same quantity and in characterizing reference materials.

3.8 analytical specificity: Ability of a measurement procedure to determine solely the measurable quantity it purports to measure.

3.9 analytical interference: Systematic error of measurement caused by an influence quantity which does not by itself produce a signal in the measuring system, but which causes an enhancement or depression of the value indicated.

3.10 influence quantity: Quantity that is not the measurand but that affects the result of the measurement. [2.7 of VIM]

3.11 measurand: Particular quantity subject to measurement. [2.6 of VIM]

4 Presentation of a reference measurement procedure

4.1 Elements of a written reference measurement procedure

The presentation of a reference measurement procedure shall comprise at least the elements listed as mandatory (M) in table 1. The order of the elements listed in table 1 may be changed and additional elements, such as an abstract, etc. may be added as appropriate.

Table 1: Elements of the presentation of a reference measurement procedure

Element	Type [1])		Subclause in this European Standard
	M	O	
Title page	I		
Contents list		I	
Foreword	I		
Warning and safety precautions	I		4.2
Introduction		I	4.3
Title	N		
Scope	N		4.4
Normative references	N		
Definitions		N	
Symbols and abbreviations		N	
Terminology		N	4.5
Principle and method of measurement	N		4.6
Check list		N	4.7
Reagents	N		4.8
Apparatus	N		4.9
Sampling and sample	N		4.10
Preparation of measuring system and analytical portion	N		4.11
Operation of measuring system	N		4.12
Data processing	N		4.13
Analytical reliability	N		4.14
Special cases	N		4.15
Validation by inter-laboratory studies	N		4.16
Reporting	N		4.17
Quality assurance		I	4.18
Bibliography (Annex)		I	4.19
Dates of authorization and revision	I		4.20

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

4.2 Warning and safety precautions

4.2.1 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.

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

a) immediately after the title of the European Standard if the danger to be encountered is due to the product being analysed, e. g. native material of biological origin;

b) in the description of the reagents, after the name of the reagent or material if the danger to be encountered is due to a particular reagent or material, e. g. a carcinogen, a radioactive material;

c) as a cautionary statement in the first clause of the practical reference measurement procedure, e. g. for a measurement using flammable gas.

Warning notes and safety precautions shall be unnumbered.

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

4.3 Introduction

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

a) the nature of the quantity measured by the reference measurement procedure in terms of system, component, and kind-of-quantity;

b) a brief statement of its role in health care, if appropriate;

c) method of measurement and rationale for its choice;

d) place in a hierarchy of measurement procedures and 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.

NOTE: The scope could include the following items:

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

b) limits for values of quantities that can be measured by the reference measurement procedure and which can depend on other components;

c) interfering components – such as drugs, metabolites, additives, microbial growth – or other interfering factors;

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) objectives of measurement for which the reference measurement procedure is suited.

4.5 Terminology

4.5.1 Concepts

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

NOTE 1: This can include, for example

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

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

c) a current term that may not 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).

NOTE 2: The clause "Terminology" is complementary to the clause "Definitions" and sometimes also to the clause "Symbols and abbreviations" (see table 1), and the terms are often incorporated in either or distributed between both.

4.5.2 Nomenclature

The names of chemical compounds, biological components, quantities, units and symbols used shall be in accordance with European or International Standards, if available, or the latest recommendations of the appropriate international organization(s) (see [20]. 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 the relevant standard or recommending organization.

4.5.3 Trivial names

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

4.6 Principle and method of measurement

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

4.6.2 The method of measurement shall be described. If appropriate, the reasons for the choice of a certain step shall be given. Essential 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 check-list shall list the items and conditions that are required to perform the measurements.

NOTE: A check-list 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 Reagents

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

NOTE: 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 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 Auxiliary equipment

Other items 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 Special laboratory requirements

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

4.8 Reagents

4.8.1 General

For a reference measurement procedure intended as a European Standard, the following introductory paragraph shall be used, if applicable:

"During the measurement, unless otherwise stated, use only reagents specified in ISO 6353-2 and -3 if listed there; if not, then use reagents of recognized analytical grade and water of at least grade 3 as defined in EN ISO 3696".

NOTE: 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(ies));

c) as far as possible, full systematic chemical or biological name for labelling with – for each property of the prepared reagent in the final form – component name, associated kind-of-property name, and value of property, possibly with a defined measure of uncertainty of measurement (see also prEN 12287);

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

1) each product used with its chemical formula (including water of crystallization), molar mass, grade (purity), or with biological description, and amount, (if necessary also human or animal origin);

2) utensils and special cleaning procedures;

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

4) acceptable performance;

e) storage;

f) shelf life;

g) disposal;

h) hazard class with symbol, R-phrases, and S-phrases (see [21] and [22]).

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

4.8.3 Critical 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) [3]). In certain cases, e. g. when the elementary entity is not known, mass concentration may be given with the unit, for example, gram per litre (g/l).

Units such as ppm = "parts per million" = 10^{-6} and ppb = "parts per billion" = 10^{-9} shall not be used.

The kind-of-quantity names "normality" and "molarity" shall be abandoned in favour of the designation "amount-of-substance concentration" (or substance concentration or amount concentration) with the elementary entity of the component indicated if necessary.

[3]) The symbols for litre 'l' and 'L' are equally acceptable.

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

a) mass concentration (in the unit kilogram per litre (kg/l) or appropriate submultiples thereof);

b) mass fraction (in the unit one (1) or kilogram per kilogram (kg/kg));

c) volume fraction (in the unit one (1) or litre per litre (l/l));

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

NOTE: The unit "enzyme unit per millilitre" (U/ml) equals 16,67 × 10^{-6} kat/l.

4.8.5 Diluting

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

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 → 1 l;

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 European Standard in terms which include the use of a patented item, the procedures given in Annex A of ISO/IEC Directives – Part 2: 1992 shall apply.

4.9 Apparatus

4.9.1 Description

Each item of apparatus shall be described by

a) name (generic and, if necessary, type);

b) essential performance characteristics.

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 results of measurements 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, environmental factors, diet, drugs, physiological exercise, timing, posture, stasis before venous blood sampling, local surface treatment, handling of primary sample.

4.10.2 Samples

Requirements for the primary sample shall be specified in terms of 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

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

4.11.1 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 manual, including the following, as appropriate:

a) warnings and safety precautions;

b) assembly;

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

d) operating mode;

e) user's preventive maintenance.

4.11.2 Calibration

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

a) type of calibration (number of calibrator values, e. g. two-point, multiple point; bracketing (see 4.11.4); standard addition);

b) method of computing a monotonic calibration function and its measures of uncertainty of measurement;

c) acceptance criteria for calibration function;

d) choice of type of calibration procedure;

e) traceability;

f) suitable calibration materials and any checks of their required specifications;

g) calibration procedure(s), for example preparation of dilutions and subsequent dilutions or standard addition technique to correct for matrix effects;

h) establishing the calibration function;

i) interval of recalibration within series (also called runs) and/or between series;

j) special precautions.

4.11.3 Types of analytical sample

The different types of analytical sample shall be listed and characterized.

NOTE: They can derive from primary sample, calibrator material, or control material including matrix material (without analyte).

4.11.4 Structure of analytical series

When 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 material(s) (if applicable);

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

c) blank material(s) (if applicable);

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 uncertainty of results.

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

4.11.5 Analytical portion

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

4.11.6 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/DIS 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) reading.

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 primary data

When the primary 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 results

The procedure to calculate the results shall include the following:

a) processing of primary 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 quantity and unit in which the result should be expressed;

d) the model for statistical treatment of measured values;

e) the complete equation used for calculation of a result, using only quantity symbols, mathematical signs, and numbers; the symbols shall be explained in a list, also stating the 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 values necessary to calculate a result, their allowable maximum difference, and the equation used;

i) the number of significant figures in the result and any rounding procedure (see also [1] in annex B).

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 results and results expressed in other kind-of-quantities and/or 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 results obtained by other procedures

If relevant for comparability, comparative data shall be given on results of measurements 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 principle of measurement, method of measurement, or details of measurement procedure.

4.14 Analytical reliability

4.14.1 Concepts, values and their use

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

NOTE: The analytical reliability of a measurement procedure can only be estimated by several analytical performance characteristics. 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 characteristic, which can be presented as a calibration curve (or analytical curve), is the response (or output signal) of the measuring system (Y axis) against the stimulus (or input signal) from materials with conventional true values of the quantity under consideration (X axis).

4.14.3 Analytical sensitivity

The analytical sensitivity shall be given.

NOTE 1: This characteristic 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 2: The term "analytical sensitivity" is not a synonym for the concept "limit of detection" (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 a measured response into a measured value of a quantity. The method of calculating the measuring function and its uncertainty measures 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 target quantity 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 unspecificity;

EXAMPLE 2:
Phosphate interferes 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 possible, recovery measurements shall be made and the results stated.

4.14.9 Error and uncertainty

The estimate of the effect of each systematic error of known cause shall be used with opposite sign as a correction added or be expressed as a correction factor or a more complex function. Uncertainties of measurement arising from the unavoidably imperfect corrections of systematic effect shall be incorporated in the uncertainty budget (see also Guide to the expression of uncertainty in measurement). It shall be an objective in designing a reference measurement procedure to eliminate all known causes of systematic error.

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

The uncertainty of measurement is inherent to the measurement procedure and shall be distinguished from effects of mistake, that is a deviation from the prescribed procedure (see 4.14.16).

4.14.10 Accuracy of measurement

The accuracy of measurement, covering trueness and precision, shall be stated in terms of one or both of the inverse measures:

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

b) an expanded uncertainty U with the coverage factor k specified ($U = k \cdot u_c$).

NOTE: As accuracy of measurement is a "qualitative" concept, a value in the form of a product of a numerical value and a unit cannot be assigned, but ordinal-scale values such as "poor" and "good" can be used.

4.14.11 Precision of measurements

The precision shall be stated as follows:

a) repeatability conditions, that is the intra-run situation;

b) intermediate precision conditions, that is a defined between-run situation;

c) reproducibility conditions where several laboratories are involved.

NOTE: As precision of measurement is a 'qualitative concept, a value in the form of a product of a numerical value and a unit cannot be assigned, but ordinal-scale values such as "poor" and "good" can be used. Inverse measures of the precision are standard deviation, variance, and coefficient of variation.

4.14.12 Repeatability standard deviation (s_r)

The repeatability standard deviation shall be stated, preferably with an uncertainty of measurement. If the value varies with the value of the quantity, 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/DIS 78-2.

4.14.13 Reproducibility standard deviation (s_R)

The value of the reproducibility standard deviation shall be stated, together, if possible, with its uncertainty of measurement. If the value varies with the value of the quantity, a table or function shall be given.

It shall furthermore be made clear whether the repeatability variation (see 4.14.12) is included or purged.

NOTE: Presentation of reproducibility statistics is given in ISO/DIS 78-2.

4.14.14 Limit of detection

The limit of detection shall be stated.

NOTE: The value is influenced by analytical sensitivity (see 4.14.3), trueness (see 4.14.10), precision (see 4.14.11), and the distribution of blank values (see 4.14.7). It should be calculated with regard to stated probabilities of analytically false negative and false positive results of measurements.

4.14.15 Lower and higher limits of determination

The lower and higher limits of determination shall be stated.

NOTE 1: The values are related to analytical sensitivity (see 4.14.3), linearity or other function (see 4.14.5), blank measurement (see 4.14.7), recovery (see 4.14.8), trueness (see 4.14.10), precision (see 4.14.11), and limit of detection (see 4.14.14).

NOTE 2: For assessing the usefulness of a reference measurement procedure for a given purpose, and especially whether the limit of detection (see 4.14.14) and lower and higher limits of determination are adequate, it is useful to indicate the lowest and highest results recorded or likely to be found in individuals with regard to factors such as sex, age, reproductive states, and relevant states of disease.

4.14.16 Sources of mistake

If investigations of the reference measurement procedure have revealed sources of mistake that are not usually expected, they shall be mentioned in a separate subclause together with remedies (see also 4.14.9).

4.15 Special cases

This element shall describe any specified alterations in the usual reference measurement procedure that are necessary to eliminate the influence of an unusual presence or absence of specific components or properties of the material to be analysed. Such alterations shall be mentioned in the "Scope" (see 4.4).

Each special case shall be treated in a clause giving

a) principle of modification;

b) any sampling change;

c) modified procedural steps;

d) calculation and/or expression of results;

e) the statistics specified in 4.14.

4.16 Validation by inter-laboratory studies

4.16.1 General

In principle, a measurement procedure shall have been validated by inter-laboratory studies before final acceptance as a reference measurement procedure. Details of the inter-laboratory studies shall be given.

NOTE 1: The validation of a candidate reference measurement procedure by planned inter-laboratory studies is a powerful way of identifying some sources of error, estimating performance characteristics, and of assessing transferability and robustness of the reference measurement procedure.

NOTE 2: The information from inter-laboratory collaborative studies should be given in an annex.

NOTE 3: The principles of organizing an inter-laboratory study and of analysing the data are detailed in the ISO 5725 series.

NOTE 4: If an inter-laboratory study is not feasible, validation can be made by applying other reference measurement procedures to the same quantity.

4.16.2 Statistics

The results of the statistical analysis of data shall include information on the following statistics as applicable for each material measured:

a) number of laboratories retained after eliminating those whose results were entirely wrong;

b) number of outlying laboratories and the reasons for elimination;

c) number of accepted results;

d) number of rejected results and reasons for rejection;

e) table of results and assumed distribution type (if applicable);

f) arithmetic mean ($\bar{x}$) and other relevant measures of location;

g) conventional true value (if available);

h) repeatability standard deviation (s_r) (see 4.14.12);

i) repeatability coefficient of variation ($s_r / \bar{x}$ or ($s_r \cdot 100 / \bar{x}$) %);

j) repeatability limit ($r_{0,95} = 2\sqrt{2}\ s_r = 2{,}8\ s_r$);

k) reproducibility standard deviation (s_R) (see 4.14.13);

l) reproducibility coefficient of variation ($s_R / \bar{x}$ or ($s_R \cdot 100 / \bar{x}$) %);

m) reproducibility limit ($R_{0,95} = 2\sqrt{2}\ s_R = 2{,}8\ s_R$).

If usual parametric statistics do not apply, distribution-free (non-parametric) statistics shall be used.

4.17 Reporting

The required items of a report of measurement shall be listed, including such analytical information as

a) identification of source of sample;

b) reference to method and/or procedure employed;

c) results with measured quantity name, numerical value, and unit of measurement;

d) statement of uncertainty of measurement;

e) observations of unusual properties of sample;

f) observations as regards unusual features of the measurement procedure or use of modifications;

g) physiological and clinical information, if relevant.

4.18 Quality assurance

If a clause on quality assurance is included, it shall discuss as appropriate:

a) internal quality control;

b) logbook(s);

c) external quality assessment.

4.19 Bibliography

In a European Standard, references supplementing the normative references (see table 1) shall be listed in an annex as a bibliography of documents which contain additional information, but which are not necessary in order to carry out the reference measurement procedure or calculate the associated results and statistics.

NOTE 1: This bibliography can include documents which:

a) only serve for information;

b) have merely served as references in the preparation of the Standard.