INTERNATIONAL STANDARD

ISO 18113-1

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In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) —

Part 1: Terms, definitions and general requirements

Dispositifs médicaux de diagnostic in vitro — Informations fournies par le fabricant (étiquetage) —

Partie 1: Termes, définitions et exigences générales

Reference number
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Contents

Page

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 18113-1 was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and* in vitro *diagnostic test systems.*

ISO 18113 consists of the following parts, under the general title In vitro *diagnostic medical devices — Information supplied by the manufacturer (labelling)*:

— *Part 1: Terms, definitions and general requirements*

— *Part 2:* In vitro *diagnostic reagents for professional use*

— *Part 3*: In vitro *diagnostic instruments for professional use*

— *Part 4:* In vitro *diagnostic reagents for self-testing*

— *Part 5:* In vitro *diagnostic instruments for self-testing*

Introduction

Manufacturers of *in vitro* diagnostic (IVD) medical devices supply users with information to enable the safe use and expected performance of their devices. Traditionally, this information has been provided in the form of labels, package inserts and user manuals, where the type and level of detail would depend on the intended uses and country-specific regulations.

The Global Harmonization Task Force (GHTF) encourages convergence of the evolution of regulatory systems for medical devices at the global level. The goal is to facilitate trade while preserving the right of participating members to address the protection of public health by regulatory means. Consistent worldwide labelling requirements offer significant benefits to manufacturers, users, patients and regulatory authorities. Eliminating differences among regulatory jurisdictions could allow patients earlier access to new technologies and treatments by decreasing the time necessary to gain regulatory compliance. See Reference [36]. This part of ISO 18113 provides a basis for harmonization of labelling requirements for IVD medical devices.

The GHTF has established guiding principles that apply to the labelling of medical devices. See Reference [36]. These principles have been incorporated into the ISO 18113 series. Of particular note, GHTF states that country-specific requirements for the content, wording and format of labels and instructions for use should be kept to a minimum, and eliminated over time as the opportunities arise.

This part of ISO 18113 contains a comprehensive list of terms and definitions necessary to develop the labelling for IVD medical devices. Internationally agreed-upon definitions of important concepts promote greater consistency in IVD medical device labelling. While the goal is to standardize the terminology used in IVD medical device labelling to the extent possible, it is also recognised that current national and regional usage by medical laboratories, healthcare providers, patients and regulatory authorities must be respected.

An obstacle to the timely and affordable availability of IVD medical devices in some countries is the requirement for information to appear in multiple languages. Wherever practical, GHTF encourages the use of standardized, internationally recognised symbols as long as safe use of the device is not compromised by diminished understanding on the part of the user. This part of ISO 18113 provides support for the use of symbols consistent with the GHTF objectives.

GHTF also encourages manufacturers to employ the most appropriate methods of delivering information. Until recently, most information had been supplied as printed materials accompanying the IVD medical device. Modern technologies enable instructions for use and technical information to be provided using a more efficient means of delivery. Information can be digitally encoded on magnetic or optical media, displayed on a screen, incorporated in the device, or even transmitted over the internet at the time of use. These advances offer users the possibility of more timely availability of critical information, such as performance changes, and offer manufacturers more effective means of disseminating the information.

The ISO 18113 series specifies requirements for information supplied by the manufacturer of IVD medical devices. It consists of five parts, allowing it to address the specific needs of professional users and self-testing users in the most appropriate manner. Furthermore, since manufacturers provide different types of information for IVD reagents and instruments, their requirements are addressed in separate parts of the ISO 18113 series.

This part of ISO 18113 is not intended to be used alone. It contains terms, definitions and general principles that apply to all parts of ISO 18113. In addition, guidelines for the terms and definitions that describe the performance characteristics of IVD medical devices are given in Annex A. This information is not repeated in the subsequent parts, so this document is indispensable to the application of ISO 18113-2, ISO 18113-3, ISO 18113-4 and ISO 18113-5.

ISO 18113-2 specifies the requirements for labels and instructions for use supplied with IVD reagents, calibrators and control materials for professional use. ISO 18113-3 specifies the requirements for labels and instructions for use supplied with IVD instruments for professional use. ISO 18113-4 specifies the

requirements for labels and instructions for use supplied with IVD reagents, calibrators and control materials for self-testing. ISO 18113-5 specifies the requirements for labels and instructions for use supplied with IVD instruments for self-testing.

Parts 1, 2 and 3 of ISO 18113 are the International Standards necessary for IVD medical devices intended for medical laboratories and other professional uses; Parts 1, 4 and 5 of ISO 18113 are the International Standards necessary for IVD medical devices intended for self-testing. However, recognising that manufacturers often provide systems comprising an instrument with dedicated reagents, these International Standards allow the flexibility to provide the necessary information in the most appropriate format for the intended users, for example, a single operator's manual for an integrated IVD medical device system.

In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) —

Part 1: Terms, definitions and general requirements

1 Scope

This part of ISO 18113 defines concepts, establishes general principles and specifies essential requirements for information supplied by the manufacturer of IVD medical devices.

This part of ISO 18113 does not address language requirements, since that is the domain of national laws and regulations.

This part of ISO 18113 does not apply to

a) IVD devices for performance evaluation (e.g., for investigational use only),

b) instrument marking,

c) material safety data sheets.

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 1000, *SI units and recommendations for the use of their multiples and of certain other units*

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

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

ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

IEC 62366, *Medical devices — Application of usability engineering to medical devices*

EN 980, *Symbols for use in the labelling of medical devices*

3 Terms and definitions

For the purposes of this document and ISO 18113, Parts 2-5, the following terms and definitions apply. However, definitions provided in national and regional regulations shall take precedence. Furthermore, while the terms and definitions in International Standards are preferred, the terms and definitions used in the information supplied by an IVD manufacturer shall be subject to the requirements of 4.6.2.

Where synonyms are given, either term may be used but the first term is preferred.

Some definitions had to be modified for relevance to IVD labelling or to conform to ISO terminology rules. In these cases, a note indicates that the definition has been adapted and gives the source.

In some cases, additional notes or modifications to existing notes were needed to clarify the application to IVD medical devices, and notes that did not apply to IVD medical devices were omitted. Such cases are not considered modifications of the definition and are not identified as “adapted”.

Common English dictionary definitions apply to non-defined concepts, such as apparatus, device, constituent, equipment, evaluation, instrument, magnitude, material, part, phenomenon, property, reaction, signal, substance and system.

See Annex A for additional terms and definitions that may be used by IVD manufacturers to describe performance claims.

3.1
accessory
article intended explicitly by its manufacturer to be used together with an IVD medical device

— to enable the IVD medical device to achieve its intended purpose or

— to augment or extend the capabilities of the IVD medical device in the fulfilment of its intended purpose

NOTE Adapted from Reference [37], 5.0, Note 3.

3.2
advisory notice
communication issued by an organization, subsequent to delivery of a medical device, to provide supplementary information and/or to advise what action should be taken in

— the use of a medical device,

— the modification of a medical device,

— the return of a medical device to its manufacturer,

— the destruction of a medical device

NOTE Issue of an advisory notice might be required to comply with national or regional regulations.

[ISO 13485:2003, definition 3.3]

3.3
analyte
constituent of a sample with a measurable property

EXAMPLES In “mass of protein in 24-hour urine”, “protein” is the analyte and “mass” is the property. In “concentration of glucose in plasma”, “glucose” is the analyte and “concentration” is the property. In both cases, the full phrase designates the **measurand** (3.39).

NOTE Adapted from ISO 17511:2003, definition 3.2.

3.4
authorized representative
any natural or legal person established within a country or jurisdiction who has received a mandate from the manufacturer to act on his behalf for specified tasks with regard to the latter's obligations under that country's or jurisdiction's legislation

NOTE 1 In the European Union, Directive 98/79/EC [38] requires the manufacturer to designate an "EC authorized representative", established in the European Community if the manufacturer is not located in the European Community.

NOTE 2 Adapted from Reference [39].

3.5
batch
lot
defined amount of material that is uniform in its properties and has been produced in one process or series of processes

NOTE 1 The material can be either starting material, intermediate material or finished product.

NOTE 2 Adapted from EN 375:2001, definition 3.2.

3.6
batch code
lot number
distinctive set of numbers and/or letters that specifically identifies a batch and permits its manufacturing, packaging, labelling and distribution history to be traced

NOTE Adapted from EN 375:2001, definition 3.3, Reference [40], 820.3 (c), and Reference [41], Section I.

3.7
biological reference interval
reference interval
specified interval of the distribution of values taken from a biological reference population

EXAMPLE The 0,95 biological reference interval for sodium ion concentration values in serum from a population of healthy male and female adults is 135 mmol/l to 145 mmol/l.

NOTE 1 A reference interval is commonly defined as the central 95 % interval. Another size or an asymmetrical location of the reference interval could be more appropriate in particular cases.

NOTE 2 A reference interval can depend upon the type of primary samples and the examination procedure used.

NOTE 3 In some cases, only one biological reference limit is important, usually an upper limit, "x", so that the corresponding biological reference interval would be less than or equal to "x".

NOTE 4 Terms such as "normal range", "normal values", and "clinical range" are ambiguous and therefore discouraged.

NOTE 5 Adapted from References [42], [43], [44] and [45].

3.8
biological reference population
reference population
group of individuals in a well-defined state of health or disease

NOTE 1 When biological reference intervals are provided by a manufacturer in the instructions for use, laboratories using the IVD medical device are responsible for verifying that the biological reference populations represent the populations serviced by the laboratories.

NOTE 2 A biological reference population can be a defined homogenous group of apparently healthy individuals or individuals with a specific medical condition. The concept allows for relating the reference interval to age, gender and ethnicity of the reference population, as appropriate.

NOTE 3 Adapted from References [42], [43], [44] and [45].

3.9
calibration
operation that, under specified conditions in a first step, establishes a relationship between the quantity values with measurement uncertainties provided by measurement standards and corresponding measurement indications with associated measurement uncertainties and, in a second step, uses this information to establish a relationship for obtaining a measurement result from an indication

NOTE 1 Calibration permits either the assignment of values of the measurands to the measurement indications provided by the measuring instrument, or the determination of a correction with respect to the values provided by the measuring instrument.

NOTE 2 Calibration is sometimes confused with adjustment of a measuring system, often mistakenly called self-calibration, or with **calibration verification** (3.10).

[ISO/IEC Guide 99:2007, definition 2.39]

3.10
calibration verification
verification of calibration
confirmation that stated trueness claims for an IVD measuring system are achieved

NOTE 1 Calibration verification requires reference materials with assigned values at concentrations appropriate for the intended use.

NOTE 2 Calibration verification is sometimes confused with **calibration** (3.9), linearity verification or routine control procedures.

3.11
calibrator
measurement standard used in the calibration of an IVD instrument or system

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

3.12
component
part of a finished, packaged and labelled IVD medical device

EXAMPLES Raw material, substance, piece, part, software, firmware, labelling or assembly.

NOTE 1 Typical kit components include antibody solutions, buffer solutions, calibrators and/or control materials.

NOTE 2 Adapted from Reference [40], 820.3(c).

3.13
control material
substance, material or article intended by its manufacturer to be used to verify the performance characteristics of an IVD medical device

[EN 375:2001, definition 3.5]

3.14
control procedure
set of operations at the point of use, described specifically, intended to monitor the performance characteristics of an IVD medical device and fulfil requirements for quality

NOTE 1 Control procedures can be intended to monitor all or part of the IVD examination process, from the collection of the sample to reporting the result of the examination.

NOTE 2 Adapted from ISO 15198:2004, definition 3.5.

3.15
distributor
person or legal entity that furthers the marketing and/or selling of a device from the original place of manufacture to the ultimate user without modifying the device, its packaging or its labelling

NOTE Adapted from Reference [46], 803.3 (g).

3.16
examination
set of operations having the object of determining the value or characteristics of a property

NOTE 1 In some disciplines (e.g., microbiology) an examination is the total activity of a number of tests, observations or measurements.

NOTE 2 Laboratory examinations that determine the value of a property are called quantitative examinations; those that determine the characteristics of a property are called qualitative examinations.

NOTE 3 In clinical chemistry, laboratory examinations have been called assays or tests.

[ISO 15189:2007, definition 3.4]

3.17
expiry date
expiration date
upper limit of the time interval during which the performance characteristics of a material stored under specified conditions can be assured

NOTE 1 Expiry dates are assigned to IVD reagents, calibrators, control materials and other components by the manufacturer, based on experimentally determined stability properties (see 3.68).

NOTE 2 Guidelines for determining the stability of IVD medical devices are found in EN 13640.

NOTE 3 Adapted from EN 375:2001, definition 3.6.

3.18
graphical symbol
visually perceptible figure used to transmit information independently of language

[ISO/IEC 80416-1:2001, definition 3.1]

3.19
harm
physical injury or damage to the health of people, or damage to property or the environment

[ISO/IEC Guide 51:1999, definition 3.3]

3.20
hazard
potential source of **harm**

[ISO/IEC Guide 51:1999, definition 3.5]

3.21
hazardous situation
circumstance in which people, property or the environment are exposed to one or more **hazards**

NOTE Incorrect IVD examination results can contribute to a hazardous situation for a patient. See ISO 14971:2007, Annex H.

[ISO/IEC Guide 51:1999, definition 3.6]

3.22
hazardous waste
waste that is potentially harmful to human beings, property or the environment

EXAMPLES Used reagent strips contaminated with human blood; reagent solution containing sodium azide; decommissioned instruments containing heavy metals.

NOTE 1 Includes waste that is flammable, combustible, ignitable, corrosive, toxic, reactive, injurious or infectious.

NOTE 2 Adapted from ISO 15190:2003, definition 3.13.

3.23
healthcare provider
individual authorized to deliver health services to a patient

EXAMPLES Physician, nurse, ambulance attendant, dentist, diabetes educator, laboratory technician, medical assistant, medical specialist, respiratory care practitioner.

NOTE Adapted from Reference [41].

3.24
immediate container
primary container
packaging that protects the contents from contamination and other effects of the external environment

EXAMPLES Sealed vial, ampoule or bottle, foil pouch, sealed plastic bag.

NOTE Does not include package liners.

[EN 375:2001, definition 3.7]

3.25
importer
person or legal entity who brings goods, or causes goods to be brought into a country from another country

NOTE 1 Importers are not permitted to repackage the goods or change their container, packaging or labelling in some jurisdictions, including the EU and USA.

NOTE 2 Adapted from Reference [46], 803.3 (m).

3.26
***in vitro* diagnostic instrument**
IVD instrument
equipment or apparatus intended by a manufacturer to be used as an IVD medical device

NOTE Adapted from EN 591:2001, definition 3.5.

3.27
***in vitro* diagnostic medical device**
IVD medical device
device, whether used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes and including reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles

NOTE This is the definition adopted by the GHTF in [47].

3.28
***in vitro* diagnostic reagent**
IVD reagent
chemical, biological or immunological components, solutions or preparations intended by the manufacturer to be used as an IVD medical device

NOTE Adapted from EN 375:2001, definition 3.9.

3.29
information supplied by the manufacturer
labelling
written, printed or graphic matter

— affixed to an IVD medical device or any of its containers or wrappers or

— provided for use with an IVD medical device,

related to identification and use, and giving a technical description, of the IVD medical device, but excluding shipping documents

EXAMPLES Labels, instructions for use.

NOTE 1 In IEC standards, documents provided with a medical device and containing important information for the responsible organization or operator, particularly regarding safety, are called "accompanying documents".

NOTE 2 Catalogues and material safety data sheets are not considered labelling of IVD medical devices.

NOTE 3 Adapted from ISO 13485:2003, definition 3.6.

3.30
instructions for use
information supplied by the manufacturer to enable the safe and proper use of an IVD medical device

NOTE 1 Includes the directions supplied by the manufacturer for the use, maintenance, troubleshooting and disposal of an IVD medical device, as well as warnings and precautions.

NOTE 2 Adapted from EN 376:2002, definition 3.9 and EN 591:2001, definition 3.3.

3.31
intended use
intended purpose
objective intent of an IVD manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information supplied by the IVD manufacturer

NOTE 1 Intended use statements for IVD labelling can include two components: a description of the functionality of the IVD medical device (e.g., an immunochemical measurement procedure for the detection of analyte "x" in serum or plasma), and a statement of the intended medical use of the examination results.

NOTE 2 This is the definition adopted by the GHTF in Reference [36].

3.32
kit
set of components that are packaged together and intended to be used to perform a specific IVD examination

NOTE 1 Kit components can include reagents (such as antibodies, enzymes, buffer and diluents), calibrators, controls and other articles and materials.

NOTE 2 Adapted from EN 375:2001, definition 3.10.

3.33
label
printed, written or graphic information placed on a medical device or its container

NOTE 1 A label permanently affixed to an IVD instrument is considered **marking** (3.37).

NOTE 2 Adapted from EN 375:2001, definition 3.12.

3.34
lay person
individual without formal training in a relevant medical field or discipline

EXAMPLE Person who performs self-testing without having a medical education.

NOTE Adapted from EN 376:2002, definintion 3.13.

3.35
limitation of the procedure
specific situation in which an IVD examination procedure might not perform as intended

NOTE 1 Factors that affect the performance of an IVD examination procedure can be physiological as well as analytical.

NOTE 2 Adapted from Reference [48].

3.36
manufacturer
natural or legal person responsible for the design, manufacture, fabrication, assembly, packaging or labelling of a medical device, for assembling a system, or adapting a medical device before it is placed on the market and/or put into service, regardless of whether these operations are carried out by that person or on their behalf by a third party

NOTE 1 Provisions of national or regional regulations could apply to the definition of manufacturer.

NOTE 2 Manufacturer includes those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking or specification development, and initial distributors of foreign entities performing these functions.

NOTE 3 A harmonized definition of "manufacturer" is being developed by the GHTF.

[ISO 14971:2007, definition 2.8]

3.37
marking
inscription, in writing or as a graphical symbol, permanently affixed to a medical device

NOTE 1 Marking is a label permanently affixed to an **IVD instrument** (3.26).

NOTE 2 Adapted from IEC 61010-2-101:2002, definition 3.106.

3.38
material safety data sheet
MSDS
document prepared in accordance with regulatory requirements for occupational safety to convey information about a hazardous chemical substance

NOTE 1 Typically describes physical properties, health hazards, toxicity, fire and reactivity properties, and provides storage and handling precautions.

NOTE 2 Material safety data sheets are not considered part of IVD medical device labelling.

NOTE 3 Adapted from Reference [49], 1910.1200 (c) and 1910.1200 (g).

3.39
measurand
quantity intended to be measured

NOTE 1 The specification of a measurand in laboratory medicine requires knowledge of the kind of quantity (e.g., mass concentration), a description of the matrix carrying the quantity (e.g., blood plasma), and the chemical entities involved (e.g., the analyte).

NOTE 2 The measurand can be a biological activity.

NOTE 3 See 3.3 for other examples of IVD measurands.

NOTE 4 In chemistry, "analyte", or the name of a substance or compound, are terms sometimes used for "measurand". This usage is erroneous because these terms do not refer to quantities.

[ISO/IEC Guide 99:2007, definition 2.3]

3.40
measurement
process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity

NOTE 1 In chemistry, "analyte", or the name of a substance or compound, are terms sometimes used for "measurand". This usage is erroneous because these terms do not refer to quantities.

NOTE 2 Measurement implies comparison of quantities or counting of entities.

NOTE 3 Measurement presupposes description of the quantity commensurate with the intended use of the measurement result, of a measurement procedure, and of a calibrated measuring system operating according to the specified measurement.

NOTE 4 The operations can be performed automatically.

[ISO/IEC Guide 99:2007, definition 2.1]

3.41
measurement method
generic description of a logical organization of operations used in a **measurement**

NOTE 1 A measurement method is used in a specific **measurement procedure** (3.44).

NOTE 2 Measurement methods can be qualified in various ways such as direct measurement method and indirect measurement method. See IEC 60050-300 for further information.

[ISO/IEC Guide 99:2007, definition 2.5].

3.42
measurement model
mathematical relation among all quantities known to be involved in a **measurement**

EXAMPLE Four-parameter logistic function for fitting sigmoidal measurement indications to calibrator concentrations in immunochemical measurement procedures.

NOTE 1 A general form of the measurement model is the equation $h(Y, X_1, K, X_n) = 0$, where Y, the output quantity in the measurement model, is the **measurand** that is to be inferred from information about input quantities in the measurement model X_1, K, X_n.

NOTE 2 In more complex cases where there are two or more output quantities, the measurement model consists of more than one equation.

NOTE 3 In clinical chemistry, measurement models have also been called calibration models.

[ISO/IEC Guide 99:2007, 2.48]

3.43
measurement principle
principle of measurement
phenomenon serving as a basis of a **measurement**

EXAMPLES

a) Ion selective electrode applied to the measurement of sodium activity;

b) Antibody affinity applied to the measurement of thyroid stimulating hormone (TSH) concentration;

c) Liquid chromatography applied to the measurement of digoxin concentration.

NOTE The phenomenon can be of a physical, chemical or biological nature.

[ISO/IEC Guide 99:2007, definition 2.4]

3.44
measurement procedure
detailed description of a measurement according to one or more measurement principles and to a given measurement method, based on a measurement model and including any calculation necessary to obtain a measurement result

NOTE 1 A measurement procedure is usually documented in sufficient detail to enable an operator to perform a measurement.

NOTE 2 A measurement procedure can include a statement concerning a target measurement uncertainty.

[ISO/IEC Guide 99:2007, definition 2.6]

3.45
measurement result
set of quantity values being attributed to a measurand together with any other available relevant information

NOTE 1 In many fields of metrology, a measurement result is expressed as a single measured quantity value and a measurement uncertainty. In laboratory medicine, measurement results are usually expressed as single measured quantity values.

NOTE 2 A measurement generally provides information about the set of quantity values, such that some are more representative of the measurand than others. This can be demonstrated in the form of a probability density function.

NOTE 3 In the traditional literature and in the previous edition of the VIM[81], measurement result was defined as a value attributed to a measurand and explained to mean a measurement indication, or an uncorrected result, or a corrected result, or an average of several values, according to the context.

[ISO/IEC Guide 99:2007, definition 2.9]

3.46
measuring interval
set of values of quantities of the same kind that can be measured by a given measuring instrument or measuring system with specified instrumental uncertainty, under defined conditions

NOTE 1 The measuring interval over which the performance characteristics of an IVD medical device have been validated has been called the reportable range.

NOTE 2 The lower limit of a measurement interval should not be confused with the detection limit (A.3.14). See A.2.8 for further information.

NOTE 3 For a discussion of the difference between interval and range, see A.2.11.

[ISO/IEC Guide 99:2007, definition 4.7]

3.47
medical device
instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,

— investigation, replacement, modification or support of the anatomy or of a physiological process,

— supporting or sustaining life,

— control of conception,

— disinfection of medical devices,

— providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body,

and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which can be assisted in its intended function by such means

[ISO 13485:2003, definition 3.7]

NOTE 1 The term medical device includes *in vitro* diagnostic medical devices.

NOTE 2 This is the definition adopted by the GHTF in Reference [37].

NOTE 3 See Clause 3 of ISO 13485:2003 for additional examples of medical devices.

3.48
metrological traceability
property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty

NOTE 1 For this definition, a reference can be a definition of a measurement unit through its practical realization, or a measurement procedure including the measurement unit for a nonordinal quantity, or a measurement standard.

NOTE 2 Metrological traceability requires an established calibration hierarchy. The sequence of measurement standards and calibrations which is used to relate a measurement result to a reference is called a traceability chain. A metrological traceability chain is used to establish metrological traceability of a measurement result, including calibrator values. See ISO 17511[16] and ISO 18153[18] for examples of traceability chains pertaining to IVD medical devices.

NOTE 3 Specification of the stated reference must include the time at which this reference was used in establishing the calibration hierarchy, along with any other relevant metrological information about the reference, such as when the first calibration in the calibration hierarchy was performed.

NOTE 4 For measurements with more than one input quantity in the measurement model, each of the quantity values should itself be metrologically traceable and the calibration hierarchy involved can form a branched structure or a network. The effort involved in establishing metrological traceability for each input quantity should be commensurate with its relative contribution to the measurement result.

NOTE 5 A comparison between two measurement standards can be viewed as a calibration if the comparison is used to check and, if necessary, correct the quantity value and measurement uncertainty attributed to one of the measurement standards.

NOTE 6 The abbreviated term traceability is sometimes used to mean metrological traceability as well as other concepts, such as sample traceability or document traceability or instrument traceability or material traceability, where the history (trace) of an item is meant. Therefore, the full term of metrological traceability is preferred if there is any chance of confusion.

[ISO/IEC Guide 99:2007, definition 2.41]

3.49
outer container
sales packaging
material used in the packaging of the immediate container or containers of an IVD medical device, which can consist of a single component, a kit or an assembly of different or identical components

NOTE Adapted from EN 375:2001, definition 3.13.

3.50
performance characteristic
metrological property
one of the parameters used to define the performance of an IVD medical device

EXAMPLES Detection limit, precision, specificity.

NOTE Information about more than one performance characteristic is usually required to evaluate the suitability of an IVD medical device for its intended medical use.

3.51
performance claim
specification of a performance characteristic of an IVD medical device as documented in the information supplied by the manufacturer

NOTE 1 This can be based upon prospective performance studies, available performance data or studies published in the scientific literature.

NOTE 2 Adapted from EN 13612:2002, definition 2.7.

3.52
performance evaluation
investigation of a device intended to become an IVD medical device for the purpose of establishing or verifying its performance claims

NOTE Adapted from EN 13612:2002, definition 2.8.

3.53
precaution
statement that alerts users to special care or activities necessary for safe and effective use of an IVD medical device or to avoid damage to the IVD medical device that could occur as a result of use, including misuse

NOTE 1 The distinction between warnings and precautions is a matter of degree, considering the likelihood and seriousness of the hazard. See the definition of **warning** (3.74).

NOTE 2 Adapted from Reference [50].

3.54
primary sample
specimen
discrete portion of a body fluid or tissue taken for examination, study or analysis of one or more quantities or characteristics to determine the character of the whole

NOTE 1 GHTF uses the term specimen in its harmonized guidance documents to mean a **sample** (3.64) of biological origin intended for examination by a medical laboratory.

NOTE 2 Adapted from Reference [51].

3.55
primary sample collection device
specimen collection device
apparatus specifically intended by an IVD manufacturer to obtain, contain and preserve a body fluid or tissue for *in vitro* diagnostic examination

NOTE 1 Includes devices intended to store a primary sample prior to examination.

NOTE 2 Includes both vacuum and non-vacuum primary sample collection devices.

NOTE 3 Adapted from Reference [38], Article 1, 2(b).

3.56
professional use
designation that an IVD medical device is intended for personnel who are qualified to perform IVD examinations through special education and training

NOTE Adapted from EN 375:2001, definition 3.14.

3.57
reactive ingredient
constituent that participates in a chemical reaction intended to detect or measure a quantity

EXAMPLES Antibodies, specific viral nucleotide sequences, enzyme substrates.

NOTE 1 Constituents such as buffers, preservatives and stabilisers that do not participate in the chemical reaction are not considered reactive ingredients.

NOTE 2 Adapted from EN 375:2001, definition 3.1.

3.58
reference material
material, sufficiently homogeneous and stable regarding one or more properties, with reference to specified properties, which has been established to be fit for its intended use in measurement or in examination of nominal properties

NOTE 1 Reference materials with or without assigned quantity values can be used for measurement precision control whereas only reference materials with assigned quantity values can be used for calibration or measurement trueness control.

NOTE 2 In a given measurement, a given reference material can only be used for either calibration or quality assurance.

NOTE 3 Reference material comprises materials embodying quantities as well as nominal properties.

Examples of reference materials embodying quantities:

EXAMPLE 1 Water of stated purity, the dynamic viscosity of which is used to calibrate viscometers.

EXAMPLE 2 Blood plasma containing a stated mass fraction of glucose, used as a calibrator.

EXAMPLE 3 Human serum without an assigned quantity value for the inherent cholesterol concentration, used only as a measurement precision control material.

Examples of reference materials embodying properties:

EXAMPLE 4 Colour chart indicating one or more specified colours.

EXAMPLE 5 DNA compound containing a specified nucleic acid sequence.

EXAMPLE 6 Urine containing 19-androstenedione.

NOTE 4 A reference material is sometimes incorporated into an IVD medical device:

EXAMPLE 1 Substance of known triple-point in a triple-point cell.

EXAMPLE 2 Glass of known optical density in a transmission filter holder.

EXAMPLE 3 Spheres of uniform size mounted on a microscope slide.

NOTE 5 A reference material, accompanied by documentation issued by an authoritative body and referring to valid procedures used to obtain a specified property value with associated uncertainty and traceability, is called a certified reference material.

EXAMPLE Human serum with assigned quantity value for the cholesterol concentration and associated measurement uncertainty, used as a calibrator or measurement trueness control material.

NOTE 6 Some reference materials have quantities that are metrologically traceable to a measurement unit outside a system of units. Such materials include measurement standards of biological origin to which International Units (IU) have been assigned by the World Health Organization.

NOTE 7 The specifications of a reference material include its material traceability, indicating its origin and processing. Requirements for the specifications of reference materials for IVD medical devices are described in ISO 15194[12].

NOTE 8 Uses of reference materials can include the calibration of a measurement system, assessment of a measurement procedure, assigning values to other materials, and quality control. See also **measurement standard** (A.3.33).

NOTE 9 Examination of a nominal property provides a nominal property value and associated uncertainty. This uncertainty is not a measurement uncertainty.

NOTE 10 ISO/REMCO (Committee on reference materials) has an analogous definition but uses the term measurement process to mean **examination** (3.16), to cover both measurement and examination of a nominal property.

[ISO/IEC Guide 99:2007, definition 5.13]

3.59
reference measurement procedure
measurement procedure accepted as providing measurement results fit for their intended 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 Requirements for reference measurement procedures for IVD medical devices are described in ISO 15193[11].

NOTE 2 Examples of the use of reference measurement procedures to assign values to IVD calibrators are given in ISO 17511[16] and ISO 18153[18].

NOTE 3 A measurement procedure used to obtain a measurement result without relation to a measurement standard for a quantity of the same kind is called a primary reference measurement procedure. See ISO/IEC Guide 99:2007, 2.8[28]).

[ISO/IEC Guide 99:2007, definition 2.7]

3.60
residual risk
risk remaining after risk control measures have been taken

NOTE Residual risks are disclosed to users in the instructions for use. See ISO 14971:2007, Annex H.

[ISO/IEC Guide 51:1999, definition 3.9]

3.61
risk
combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999, definition 3.2]

3.62
risk control measure
action taken to reduce or maintain risks within specified levels

NOTE 1 Risk control measures based on labelling are called information for safety in ISO 14971 and are considered the least effective risk control option in order of risk management priority. Labelling intended as information for safety includes

— instructions for use (see 3.30),

— limitations of the procedure (see 3.35),

— precautions (see 3.53),

— warnings (see 3.74).

NOTE 2 General guidance on providing information for safety is provided in Annex J of ISO 14971:2007. General guidance for evaluating information for safety as a risk control measure, including review of warnings and review of the operating instructions, is provided in D.7 of ISO 14971:2007.

NOTE 3 Specific guidance pertaining to information for safety of IVD medical devices is provided in Annex H of ISO 14971:2007.

NOTE 4 Derived from ISO 14971:2007, definition 2.19.

3.63
safety
freedom from unacceptable risk

[ISO/IEC Guide 51:1999, definition 3.1]

3.64
sample
one or more representative parts taken from a system, which are intended to provide information on the system

EXAMPLE A portion of serum taken from a **primary sample** (3.54) of coagulated blood.

NOTE Adapted from ISO 15189:2007, definition 3.16.

3.65
self-testing
examination performed by a layperson to evaluate an individual's health status

NOTE 1 Typically performed in a home or other environment outside a healthcare institution without supervision by a healthcare professional.

NOTE 2 Adapted from the definition of “device for self-testing” in Reference [38].

3.66
shelf-life
period of time until the expiry date during which an IVD reagent in its original packaging maintains its stability under the storage conditions specified by the manufacturer

NOTE 1 **Stability** (3.68) and **expiry date** (3.17) are related concepts.

NOTE 2 Adapted from EN 375:2001, definition 3.16.

3.67
spare part
component intended to replace an identical or similar component of an instrument or other apparatus without affecting its functionality

3.68
stability
ability of an IVD medical device to maintain its performance characteristics within the limits specified by the manufacturer

NOTE 1 Stability applies to

— IVD reagents, calibrators and controls, when stored, transported and used in the conditions specified by the manufacturer,

— reconstituted lyophilised materials, working solutions and materials removed from sealed containers, when prepared, used and stored according to the manufacturer's instructions for use,

— measuring instruments or measuring systems after calibration.

NOTE 2 Stability of an IVD reagent or measuring system is normally quantified with respect to time

— in terms of the duration of a time interval over which a metrological property changes by a stated amount or

— in terms of the change of a property over a stated time interval.

NOTE 3 Adapted from "stability of a measuring instrument" in ISO/IEC Guide 99:2007[28], 4.19.

3.69
training
operator-oriented, application-specific instruction required for the safe and proper use of an IVD medical device

NOTE Adapted from IEC 60601-1-6:2006, definition 2.208.

3.70
trueness control material
reference material that is used to assess the bias of a measuring system

[ISO 17511:2003, definition 3.32]

3.71
use error
act or omission of an act that has a different medical device response to that intended by the manufacturer or expected by the operator

NOTE 1 Use error includes slips, lapses and mistakes.

NOTE 2 IEC 62366:2007, Annexe B and D.1.3, give a discussion and examples of use errors.

[IEC 62366:2007, definition 2.12]

3.72
validation
verification, where the specified requirements are adequate for an intended use

EXAMPLE A measurement procedure for creatinine concentration in human serum can also be validated for the measurement of creatinine concentration in human urine.

NOTE ISO 9000:2005, definition 3.8.5, defines validation as confirmation, through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled.

[ISO/IEC Guide 99:2007, definition 2.45]

3.73
verification
provision of objective evidence that a given item fulfils specified requirements

EXAMPLE 1 Confirmation that a given reference material as claimed is homogeneous for the quantity value and measurement procedure concerned, down to a measurement portion having a mass of 10 mg.

EXAMPLE 2 Confirmation that performance properties or legal requirements of a measuring system are achieved.

EXAMPLE 3 Confirmation that a target measurement uncertainty can be met.

NOTE 1 The item can be, e.g., a process, measurement procedure, material, compound or measuring system.

NOTE 2 The specified requirements can be, e.g., that a manufacturer's claims or specifications are met.

NOTE 3 In legal metrology, verification pertains to the examination and marking and/or issuing of a verification certificate for a measuring instrument.

NOTE 4 Verification should not be confused with **calibration** (3.9) or **validation** (3.72).

NOTE 5 In chemistry, verification of identity of entity involved, or of activity, requires a description of the structure or properties of that entity or activity.

NOTE 6 ISO 9000:2005, definition 3.8.4, defines verification as confirmation, through the provision of objective evidence that specified requirements have been fulfilled.

[ISO/IEC Guide 99:2007, definition 2.44]

3.74
warning
statement that alerts users about a situation that, if not avoided, could result in hazards or other serious adverse consequences from the use of an IVD medical device

NOTE 1 The designation of a hazard alert as a warning is reserved for the most significant consequences.

NOTE 2 The distinction between a warning and a **precaution** (3.53) is a matter of degree, considering the likelihood and seriousness of the **hazard** (3.20).

NOTE 3 Use includes **use errors** (3.71) and reasonably foreseeable misuse. See ISO 14971 and IEC 62366 for discussions of these concepts.

NOTE 4 Adapted from Reference [50].

4 General requirements for information supplied by the manufacturer

4.1 General

4.1.1 The format, content, location and accessibility of information supplied by the manufacturer shall be appropriate to the particular device and its intended users. Suitability of the information supplied by the manufacturer is assessed as part of the design validation.

4.1.2 Information on labels and in the instructions for use shall be legible for the intended lifetime of the device, accessory, kit or component. Legibility of the information on labels and in the instructions for use is assessed as part of the design verification.

NOTE Legibility depends on quality of print, font type, point size, etc.

4.1.3 Information supplied by the manufacturer should include a statement or symbol that encourages the user to carefully read the instructions for use before attempting to use the device.

NOTE This is a requirement in Japan.

4.1.4 This part of ISO 18113 is not intended to be used alone. It is intended to be used in conjunction with ISO 18113-2, ISO 18113-3, ISO 18113-4 and/or ISO 18113-5 as relevant to the device.

4.1.5 Where this part of ISO 18113, ISO 18113-2, ISO 18113-3, ISO 18113-4 and/or ISO 18113-5 state a requirement, the requirement applies unless the manufacturer justifies and documents that the requirement is not appropriate to the IVD medical device.

The justification may be based on risk analysis, human factors evaluation, technical assessment or documentation that the requirement does not apply.

4.2 Language

4.2.1 The information supplied by the manufacturer shall be written in the language(s) required by the countries in which the IVD medical device is distributed.

4.2.2 The device name and the manufacturer's name and address are not required to be expressed in multiple languages.

4.3 Symbols and identification colours

4.3.1 Graphical symbols should be used, where appropriate.

4.3.2 Symbols and identification colours shall conform to International Standards when available. When using symbols, the requirements of ISO 15223-1 and EN 980 apply.

4.3.3 When no standard exists, or if a symbol might not be understood by the intended user, the symbols and identification colours shall be described in the information supplied by the manufacturer.

4.4 Values and nomenclature

4.4.1 Numerical values shall be provided in units generally recognised by the intended users, preferably in accordance with ISO 1000.

EXAMPLES Values representing concentrations, contents, volumes, results, reference intervals, environmental parameters.

4.4.2 Examination procedures and analytes shall be named using terms generally recognised by the intended users, preferably according to internationally recognised sources.

4.5 Microbiological state

The microbiological state shall be specified, where appropriate.

EXAMPLE Sterile, microbiologically controlled.

4.6 Instructions for use

4.6.1 Instructions for use shall be provided unless the manufacturer shows by risk analysis that the IVD medical device can be used safely as intended without them. The requirements of ISO 14971 apply.

NOTE National or regional regulations can require instructions for use for all IVD medical devices.

4.6.2 Instructions for use shall be written using terms likely to be understood by the intended users.

4.6.3 The order of information presented in the instructions for use shall be determined by the manufacturer, taking into account the intended user.

4.6.4 The date of issue or the latest revision of the instructions for use and an identification number shall be given.

4.6.5 The instructions for use may be on the outer container, in an operator's manual or combined with the instructions for use for a related instrument, reagent or system.

4.6.6 Instructions for use, either in paper or non-paper format, shall be supplied with the IVD medical device or be provided separately from the device by other means appropriate for the intended users.

4.6.7 The distribution of the instructions for use by other means shall be appropriate for the intended user. Other means of distribution may include the following:

a) service/sales/support organizations;

b) internet website;

c) return telefax system;

d) an electronic databank;

e) coded format explained in a manual.

EXAMPLES Barcode, computer chip.

4.6.8 If the instructions for use are not provided with the device, the manufacturer shall ensure that the user has the following:

a) instructions on how to obtain the information;

b) access to the correct version of the instructions for use;

c) as a minimum, information to cover safe handling and storage prior to use.

4.7 Changes to the IVD medical device

4.7.1 The manufacturer shall draw the user's attention to any changes in the intended use of the IVD medical device, or to any changes in the information required to use the device properly and safely, and to where the pertinent information can be found.

4.7.2 Advisory notices may be issued by the manufacturer to provide supplementary information subsequent to delivery of the IVD medical device, and/or to advise as to what action should be taken in regard to the use, modification, return or destruction of the IVD medical device. The requirements of ISO 13485 apply.

NOTE National or regional regulations can apply to the issue of an advisory notice.

4.8 Disclosure of residual risks

4.8.1 Users shall be informed of known safety hazards and the residual risks. The requirements of ISO 14971 and IEC 62366 apply.

EXAMPLES Warning and precaution statements, limitations of the procedure.

4.8.2 Hazardous situations that could result from use errors, reasonably foreseeable misuse and uses not recommended by the manufacturer shall also be identified.

4.8.3 Warnings and precautions may take the form of symbols.

4.9 Identification of components

4.9.1 Component names shall be given consistently in the instructions for use, the outer container and, if applicable, the immediate container.

4.9.2 In the case of a reagent kit, each component shall be identified by name, letter, number, symbol, colour or graphics in the same manner in all of the information supplied by the manufacturer.

4.10 Assistance

The user shall be given instructions on how to obtain assistance. Such instructions may direct the user, for example, to a telephone number listing/directory, to a company website, or to another such resource, where information on access to local assistance can be obtained.

Annex A
(informative)

Performance characteristics of IVD medical devices

A.1 General considerations

A.1.1 Current trends in metrology

The International Vocabulary of Basic and General Terms in Metrology[81] (VIM) has undergone major revision. Metrology, the science of measurement and its application, includes measurements in laboratory medicine and related fields. The new VIM, now called ISO/IEC Guide 99[28], has been expanded to address measurements in these fields, as well as to include concepts that relate to metrological traceability, measurement uncertainty, and nominal properties (the subject of qualitative examination procedures).

ISO/IEC Guide 99 reflects the evolution of the treatment of measurements from the error approach (also called the true-value approach) traditionally used in clinical chemistry to a contemporary approach based on the uncertainty of measurement results. The following discussion is extracted from the Introduction to ISO/IEC Guide 99:2007.

In the error approach, a measurand can be described by a single true value that is consistent with the definition of the measurand. The objective of measurement is to determine an estimate of the true value that is as close as possible to that single true value. The deviation from the true value is composed of random and systematic errors. The two kinds of errors, assumed to be always distinguishable, shall be treated differently. No rule can be derived on how they combine to form the total error of any given measurement result, usually taken as the estimate. Usually, only an upper limit of the absolute value of the total error is estimated, sometimes loosely named uncertainty.

In the uncertainty approach, the objective of measurement is not to determine a true value as closely as possible. Rather, the information from measurement only permits assignment of an interval of reasonable values to the measurand. Additional relevant information may reduce the range of the interval of values that can reasonably be attributed to the measurand, but even the most refined measurement cannot reduce the interval to a single value because of the finite amount of detail in the definition of a measurand. This definitional uncertainty therefore sets a minimum limit to any measurement uncertainty. The interval can be represented by one of its values, called a measured quantity value.

The uncertainty approach is detailed in the GUM[82], now called ISO/IEC Guide 98-3[27], which focuses on the mathematical treatment of measurement uncertainty through an explicit measurement model under the assumption that the measurand can be characterized by an essentially unique value. The GUM retained the concept of true value for describing the objective of measurement, although the adjective “true” is considered to be redundant. In this annex, the concept and term of “true value” are also retained because of common usage. Moreover, the GUM as well as IEC documents provide guidance on the Uncertainty Approach in the case of a single reading of a calibrated instrument, a situation commonly encountered in laboratory medicine.

The focus on measurements with single readings is particularly relevant to laboratory medicine because it permits the investigation of whether quantities vary in time by demonstrating whether measurement results are compatible. The IEC view also allows non-negligible definitional uncertainties, a situation also found in the calibration of IVD medical devices. The validity of the measurement results is highly dependent on the metrological properties of the instrument as demonstrated by its calibration. The interval of values offered to describe the measurand is the interval of values of measurement standards that would have given the same indications.

When updating the VIM, it was taken for granted that there is no fundamental difference in the basic principles of measurement, whether the measurements are made in physics, chemistry, laboratory medicine, biology or

engineering. ISO/IEC Guide 99 also attempts to meet the conceptual needs of measurements in fields such as biochemistry, food science, forensic science and molecular biology. Although some metrological concepts and terms used in laboratory medicine are in transition and performance characteristics are being defined more clearly and consistently, it is anticipated that the error approach to evaluating systematic and random error will coexist with the newer uncertainty approach for some time. See References [27], [52], [53].

A.1.2 Guidelines for IVD labelling

Changes in measurement concepts and terminology can create a dilemma for IVD medical device manufacturers. Traditional terms and definitions are still used by medical laboratories in many parts of the world, and may even be prescribed by law or regulation. Moreover, for self-testing IVD medical devices, technical concepts need to be explained in familiar terms appropriate for lay persons.

Because a basic principle of labelling requires manufacturers to provide technical information in terms likely to be understood by the intended users (see Reference [36]), the IVD medical device industry cannot unilaterally adopt new terms and definitions for the sake of harmonization with other industries. Changes not only require a consensus among laboratories, regulatory authorities and manufacturers, but also physicians who ultimately use the IVD examination results. New terms need to be introduced carefully and systematically, and in the end it is up to each manufacturer to determine the appropriate labelling and take the necessary steps to minimize the risks that accompany labelling changes. A significant transition period may be necessary to achieve full consensus and implementation.

In this annex, terms and concepts from the uncertainty approach are introduced while those from the traditional error approach are retained, since the latter approach is still widely used in laboratory medicine. Some familiar terms have been deprecated to avoid confusion, and their continued use in IVD labelling is discouraged.

Manufacturers of IVD medical devices for self-testing face a special challenge when attempting to describe analytical performance in terms understandable by a lay person. While professional users may need to understand metrological concepts and evaluate performance data, this information is less important to lay users than information that informs them when the device is not performing correctly. The use of simplified terms to inform lay users of the expected performance characteristics of their device is encouraged, but specific guidance is beyond the scope of this annex.

The definitions, recommendations and guidelines in this annex are provided to assist manufacturers in describing the performance characteristics of their IVD medical devices while furthering the goal of harmonizing the information provided by the manufacturer. The primary sources of terms and definitions used in this annex are: (1) ISO 5725-1[5], which describes a unified concept of accuracy (trueness and precision) of measurement results; (2) ISO 3534-1[3] and ISO 3534-2[4], the vocabulary standards for statistical terminology; (3) ISO/IEC Guide 99[28], which represents a consensus among the leading international organizations in the field of metrology, including laboratory medicine; (4) IEC 60050[20], International Electrotechnical Vocabulary, IEV; (5) *IUPAC-IFCC Glossary of Terms in Quantities and Units in Clinical Chemistry*[54] and other IUPAC terminology compendia, References [55], [56], [57] and (6) various GHTF Guidance Documents and the regulations of the GHTF members.

A.2 Performance characteristics

A.2.1 General

The following section expands on the relationships among the performance characteristics of IVD medical devices and discusses the effects of changes in metrological terminology on the use of specific performance characteristics in the instructions for use. It is intended to help IVD manufacturers decide the appropriate terms to use in describing the performance of their products.

A.2.2 Measurement trueness

Measurement trueness (A.3.34) is the performance characteristic (3.50) representing lack of systematic measurement error (A.3.54) in a series of measurement results (3.45) from a homogeneous sample (3.64). Trueness is a qualitative concept, but measurement bias (A.3.25) – a measurable quantity inversely related to trueness – can be evaluated. The evaluation of bias requires a suitable reference material (3.58) or reference measurement procedure (3.59) that can be used to determine a reference quantity value (A.3.50) of the measurand (3.39).

Metrological traceability (3.48) of calibrator values to a reference quantity value is an attribute that provides medical laboratories with an assurance that measurement trueness is suitable for its intended use. Claims of measurement trueness should be accompanied by a statement describing the metrological traceability of the calibrator values.

See Reference [59] for information about the evaluation of trueness. See References [16], [18] and [60] for information about metrological traceability in laboratory medicine.

A.2.3 Measurement precision

Measurement precision (A.3.29) is the performance characteristic (3.50) representing the random measurement error (A.3.48) in a series of measurement results (3.45) from a homogeneous sample (3.64). Precision is a qualitative concept. For its numerical expression, the term imprecision is used, which is the dispersion of results of measurements obtained under stipulated conditions expressed as a standard deviation (A.3.52) and/or coefficient of variation. See Reference [61].

The magnitude of the standard deviation of the measurement results depends on which factors were allowed to vary and thereby affect the measurements. Precision has been defined at two extreme sets of conditions: repeatability (A.3.30), when the main controllable factors are kept constant, and reproducibility (A.3.31), when the main controllable factors are allowed to vary.

Analyst/operator, measuring instrument, measurement method, reagent lot, calibration material, location, environmental conditions and time are factors that can vary and contribute to measurement imprecision.

Precision between the extremes of repeatability and reproducibility is called intermediate measurement precision (A.3.20). Because the intermediate precision standard deviation depends on the factors and conditions that affect the measurement results, intermediate precision is a meaningful performance characteristic only when such factors and conditions are specified.

These concepts of precision are not new to medical laboratories. Repeatability is commonly called within-run or intra-series precision, and reproducibility is called laboratory-to-laboratory or inter-laboratory precision. Intermediate precision is estimated from variance components using statistical methods such as Analysis-of-Variance (ANOVA).

See Reference [62] for information about the evaluation of the precision of a measurement procedure.

A.2.4 Measurement accuracy

Measurement accuracy (A.3.24) has historically been used with two different meanings. The concept has not only been applied to individual measurement results, but also to measuring systems. This dual usage creates ambiguity and confusion.

In the first usage, the measurement error (A.3.27) associated with a single measurement result (3.45) is the difference between the measurement result and a true quantity value (A.3.57) assigned to the sample. The measurement error includes a systematic measurement error (A.3.54) component estimated by measurement bias (A.3.25) and a random measurement error (A.3.48) component estimated by a standard deviation. Thus the accuracy of a measurement result is a combination of trueness and precision.

In the second usage, the measurement error associated with a measuring system is the difference between the average of a large number of measurement results of the same homogeneous material and a true value

assigned to the material. The error associated with the average measurement result only includes a systematic error component (bias), and therefore it is related to the term trueness.

To resolve this inconsistent usage, the term “accuracy” should be reserved for individual measurement results. Accuracy is a qualitative concept, but the inaccuracy of a measurement result can be expressed by measurement uncertainty (A.3.35). See A.2.5 for further discussion of measurement uncertainty.

In certain limited circumstances it is necessary to characterize the performance of a measuring system in terms of its overall ability to produce accurate results. For example, users of IVD medical devices intended for self-testing need a simple performance characteristic to compare the usefulness of IVD medical devices. A term called “system accuracy” was derived from accuracy of a measuring instrument in 5.18 of VIM 1993, which was defined as the “ability of a measuring instrument to give responses close to a true value”. The term system accuracy is used in 3.24 of ISO 15197:2003, for evaluating glucose monitoring systems and in 3.38 of ISO 17593:2007, for evaluating oral anticoagulation monitoring systems, and is only intended for self-testing medical devices. The method for evaluating system accuracy is based on determining the uncertainty of the measurement results.

See ISO 15197 and ISO 17593 for information about the evaluation of system accuracy of self-testing IVD medical devices.

A.2.5 Measurement uncertainty

A current trend among analytical chemistry laboratories is to report measured quantity values accompanied by estimates of their measurement uncertainty (A.3.35). Although reporting measurement uncertainty is not a common practice in medical laboratories, ISO 15189[9] requires laboratories to determine and document the uncertainty of their measurement results and ISO 17511[16] requires manufacturers of IVD calibrators to determine the measurement uncertainties of their calibrator values and provide the information to users upon request.

Historically, the reliability of measurement procedures in laboratory medicine has been primarily characterized in terms of random measurement error (A.3.48) and systematic measurement error (A.3.54), as imprecision and bias, respectively. A presumption underlying the uncertainty approach is that the type of error is not important to the user of a measurement result, because it is the net effect of all the errors that determines the inaccuracy of that result. This concept can apply to applications that involve comparison of patients’ results to clinical reference values, such as biological reference intervals and risk limits established from clinical studies. However, there are situations where random error is more important than systematic error, such as when a current value is compared to a previous value from the same patient, particularly when measurements are performed by the same laboratory. For applications that involve monitoring a diagnostic marker for changes over time, medical laboratories need to know the types of error associated with their measurement procedures so they can understand when an observed change is significant.

Measurement uncertainty includes all components of variation throughout the entire traceability chain that could affect the measurement of the patient’s sample, starting with the uncertainty of the reference values, adding the uncertainties inherent in the manufacturer’s process for assigning values to calibrators supplied with IVD medical devices, and ultimately including the uncertainties introduced by the examination procedure of the medical laboratory. This concept is relatively new in laboratory medicine, and its full worldwide implementation is expected to take years and require significant educational efforts.

The concept of measurement uncertainty is described in ISO/IEC Guide 98-3[27]. See References [52] and [53] for guidelines for calculating the uncertainty of measurement results. Guidelines for calculating the uncertainty of patients’ results by medical laboratories are being developed. See References [19] and [63].

A.2.6 Analytical specificity

In laboratory medicine, the term analytical specificity (A.3.4) has been used to describe the ability of a measurement procedure to detect or measure only the measurand in the presence of other quantities present in the sample. The full term analytical specificity is preferred to avoid confusion with diagnostic specificity (see A.3.16).

The analytical specificity of a measurement procedure is typically described by a list of the potentially interfering quantities that were evaluated, with the degree of observed analytical interference (A.3.2) given at medically relevant concentration values. Although ISO/IEC Guide 99 has replaced the term specificity with selectivity, analytical specificity has been retained in this part of ISO 18113 as the preferred term for IVD labelling.

See Reference [64] for information about the evaluation of analytical specificity and determining the effects of interfering quantities.

A.2.7 Analytical sensitivity

In laboratory medicine, analytical sensitivity (A.3.3) has been used with two different but related meanings: (1) the smallest difference in concentration that can be detected with confidence; (2) the smallest quantity that can be detected with a specified confidence. There is an international consensus that the term should be restricted to the first usage and that detection limit should be used for the second usage. See Reference [28].

Analytical sensitivity – in the first usage – is not a relevant performance characteristic for most IVD medical devices, and therefore its inclusion in the instructions for use is not necessary. To avoid confusion, the term analytical sensitivity should be avoided in IVD labelling.

If analytical sensitivity is used in IVD labelling, it should be accompanied by an explanation that it means the ability of a measurement procedure to discriminate between two concentrations of a measurand. Analytical sensitivity is represented by the slope of the calibration curve according to the IUPAC definition [55].

Some regulatory jurisdictions still use the older terminology. For example, the EU Common Technical Specifications (CTS) state that “analytical sensitivity . . . may be expressed as the limit of detection: i.e. the smallest amount of the target marker that can be precisely detected” – see Reference [65]. In this case, since analytical sensitivity and limit of detection are treated as synonyms, manufacturers can use detection limit in their labelling. The CTS definition of the limit of detection is consistent with the definition of detection limit in ISO/IEC Guide 99 [28].

A.2.8 Detection limit and quantitation limit

The term detection limit (A.3.14) is used to describe the lowest value of measurand that an examination procedure can report as present with a specified level of confidence. This has also been referred to as the minimum detectable concentration.

The term quantitation limit (A.3.44) is used to describe the lowest value of measurand that an examination procedure can measure with a specified measurement uncertainty. It has also been referred to as the lower limit of determination, the lower limit of quantitation, the lower limit of measurement, and functional sensitivity.

The term functional sensitivity was originally introduced to describe the lowest concentration of thyrotropin that can be measured with the precision required for its medical use, which was set at 20 % (coefficient of variation), see Reference [66]. The term does not offer any advantage over quantitation limit. Since the term perpetuates a deprecated usage of sensitivity, it is therefore discouraged in IVD labelling.

See Reference [67] for information about the evaluation of the detection limit and the quantitation limit.

A.2.9 Linearity of a measuring system

Linearity of a measuring system (A.3.21) describes the ability of either the measurement indications (A.3.28) or the measurement results (3.45) to fit a straight line with respect to the assigned values of the samples. Linearity of measurement results obtained from IVD examination procedures is commonly evaluated after any linearization algorithm has been applied to the measurement indications.

Non-linearity is a contributor to systematic measurement bias (A.3.25). There is no single statistic that can represent an acceptable degree of non-linearity.

See Reference [68] for information about determining and verifying the linearity of a measuring system.

A.2.10 Diagnostic performance characteristics

IVD examination procedures may be characterized by their diagnostic specificity (A.3.16), which indicates the effectiveness of an examination in correctly classifying patients that do not have a particular disease or condition, and their diagnostic sensitivity (A.3.15), which indicates the efficiency of the examination in correctly identifying patients who have a particular disease or condition. The diagnostic specificity and diagnostic sensitivity depend on the choice of cut-off value (A.3.13) for the examination.

IVD examination procedures may also be characterized by their predictive value (A.3.42). A positive predictive value indicates the effectiveness of an examination procedure in separating true positive examination results from false positive examination results for a given target condition in a given population. A negative predictive value indicates the effectiveness of an examination procedure in separating true negative examination results from false negative examination results for a given target condition in a given population. The predictive value generally depends on the prevalence of the disease or condition in the population of interest.

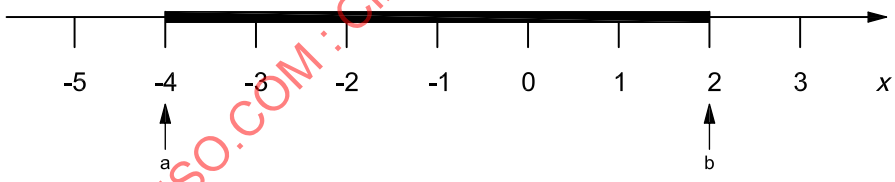
See Reference [71] for further discussion of diagnostic performance characteristics. See References [61] and [69] for information about the selection of a cut-off value and the evaluation of diagnostic specificity, diagnostic sensitivity and predictive value.

A.2.11 Interval and range

The terms interval and range are used with specific meanings. The following examples, reproduced from ISO/IEC Guide 99:2007, illustrate the concepts.

The term interval is used together with the symbol $[a, b]$ to denote the set of real numbers x for which $a \leqslant x \leqslant b$, where a and $b > a$ are real numbers. The term interval is used for a closed interval. The symbols a and b denote the end-points of the interval $[a, b]$.

For example, the interval [–4, 2] can be illustrated as follows:



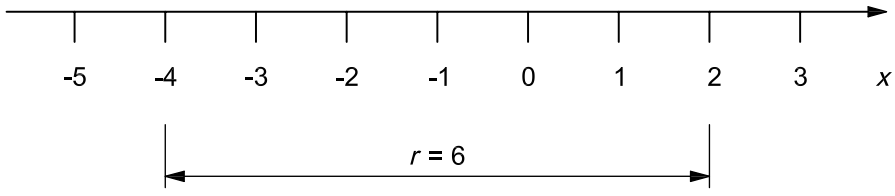
a End-point a = –4

b End-point b = 2

The two end-points 2 and –4 of the interval [–4, 2] can be stated as -1 ± 3; however, this expression does not denote the interval [–4, 2].

The range of the interval $[a, b]$ is the difference $b - a$ and is denoted by $r[a, b]$.

For example, the range $r[-4, 2] = 2 - (-4) = 6$, as illustrated below.



A.3 Additional statistical and analytical terms

The following definitions were taken from international and national sources, but some have been adapted to clarify the application to IVD medical devices or to conform to ISO vocabulary rules. Such modifications are not intended to alter the fundamental meaning of the terms. Consult the cited reference for the original definition.

The definitions and terms in this part of ISO 18113, as well as their formats, comply as far as possible with the terminology rules outlined in ISO 704[1], ISO 1087-1[2] and ISO 10241[8]. In particular, the substitution principle allows a term referring to a concept defined elsewhere in this part of ISO 18113 to be replaced by the definition corresponding to that term, without introducing contradiction or circularity.

Multiple terms for the same concept are permitted. If more than one term is given, the first term is generally preferred for use in laboratory medicine. If both terms are in bold-faced type, either term is considered acceptable for use. However, many terms in ISO/IEC Guide 99 are now prefaced by qualifiers such as measurement (e.g., measurement precision and measurement results), and the full terms are retained as the preferred terms in this part of ISO 18113. If the meaning is clear to the intended users, such terms may be used without the qualifiers.

A.3.1
adjustment of an IVD instrument
adjustment
set of operations carried out on an IVD instrument so that it provides prescribed measurement indications corresponding to given values of a quantity to be measured

NOTE 1 Types of adjustment can include zero adjustment, offset adjustment and span adjustment (sometimes called gain adjustment).

NOTE 2 Adjustment of an IVD instrument should not be confused with **calibration** (3.9), which is a prerequisite for adjustment.

NOTE 3 After an adjustment, usually an IVD instrument must be recalibrated.

NOTE 4 Adapted from ISO/IEC Guide 99:2007, definition 3.11.

A.3.2
analytical interference
interference
systematic effect on a 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

NOTE Interference with measurement results is related to the concept of **analytical specificity** (A.3.4). The more specific the measurement procedure with respect to other constituents of the sample, the less susceptible it is to analytical interference by these compounds.

[ISO 15193:2002, definition 3.9]

A.3.3
analytical sensitivity
sensitivity of a measurement procedure
quotient of the change in a measurement indication and the corresponding change in a value of a quantity being measured

NOTE 1 The sensitivity of a measurement procedure can depend on the value of the quantity being measured.

NOTE 2 The change considered in the value of the quantity being measured must be large compared with the resolution.

NOTE 3 The analytical sensitivity of a measuring system is the slope of the calibration curve.

NOTE 4 Analytical sensitivity should not be used to mean **detection limit** (A.3.14) or **quantitation limit** (A.3.44), and should not be confused with **diagnostic sensitivity** (A.3.15).

[ISO/IEC Guide 99:2007, definition 4.12]

A.3.4
analytical specificity
selectivity of a measurement procedure
capability of a measuring system, using a specified measurement procedure, to provide measurement results for one or more measurands which do not depend on each other nor on any other quantity in the system undergoing measurement

EXAMPLE Capability of a measuring system to measure the concentration of creatinine in blood plasma by the alkaline picrate procedure without interference from the glucose, urate, ketone, or protein concentrations.

NOTE 1 Lack of analytical specificity is called **analytical interference** (A.3.2).

NOTE 2 Lack of analytical specificity in immunochemistry measurement procedures can be due to **cross-reactivity** (A.3.12).

NOTE 3 Specificity of a measurement procedure should not be confused with **diagnostic specificity** (A.3.16).

NOTE 4 ISO/IEC Guide 99:2007 uses the term selectivity for this concept instead of specificity.

NOTE 5 Adapted from ISO/IEC Guide 99:2007, definition 4.13.

A.3.5
blank indication
indication obtained from a phenomenon, body or substance similar to the one under investigation, but for which a quantity of interest is supposed not to be present, or is not contributing to the indication

[ISO/IEC Guide 99:2007, definition 4.2]

A.3.6
calibration curve
expression of the relation between indication and corresponding measured quantity value

NOTE A calibration curve expresses a one-to-one relationship that does not supply a measurement result as it bears no information about the measurement uncertainty.

[ISO/IEC Guide 99:2007, definition 4.31]

A.3.7
calibration hierarchy
sequence of calibrations from a reference to the final measuring system, where the outcome of each calibration depends on the outcome of the previous calibration

NOTE 1 Measurement uncertainty necessarily increases along the sequence of calibrations.

NOTE 2 The elements of a calibration hierarchy are one or more measurement standards (including calibrators) and measuring systems operated according to measurement procedures.

NOTE 3 For this definition, the “reference” can be a definition of a measurement unit through its practical realization, or a measurement procedure or a measurement standard.

NOTE 4 A comparison between two measurement standards can be viewed as a calibration if the comparison is used to check and, if necessary, correct the quantity value and measurement uncertainty attributed to one of the measurement standards.

[ISO/IEC Guide 99:2007, definition 2.40]

A.3.8
carryover
introduction of material into a reaction mixture to which it does not belong

EXAMPLE Part of a sample, reagent, diluent or wash solution which is transferred from one container or from one reaction mixture to another one during an examination.

NOTE Adapted from Reference [55].

A.3.9
commutability of a reference material
property of a reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two given measurement procedures, and the relation obtained among the measurement results for other specified materials

NOTE 1 The reference material in question is usually a calibrator and the other specified materials are usually routine samples.

NOTE 2 The measurement procedures referred to in the definition are the one preceding and the one following the reference material (calibrator) in question in a calibration hierarchy. See ISO 17511 for further information.

NOTE 3 The stability of commutable reference materials is monitored regularly.

[ISO/IEC Guide 99:2007, definition 5.15]

A.3.10
concentration
substance concentration
amount-of-substance of a component divided by the volume of the system

NOTE 1 Unless mass, volume or number concentration is specified, the term concentration is presumed to mean substance concentration.

NOTE 2 The unit “mole per litre” is recommended for clinical chemistry. Use of the term “molarity” for this quantity is not recommended.

NOTE 3 Use of the term “level” as a synonym for concentration is deprecated.

NOTE 4 In describing a quantity, concentration must be clearly differentiated from content.

NOTE 5 The amount-of-substance of a sample or system is the physical quantity in proportion to the number of elementary entities present. The elementary entities can be atoms, molecules, ions, electrons or particles, the choice being dependent upon context and must be stated.

NOTE 6 The SI unit for amount-of-substance is the mole (mol), which is defined as the amount of substance that has an equal number of elementary entities as there are atoms in 0,012 kg (or 12 g) of carbon-12. That number is the Avogadro constant, NA, which has a value of $6{,}022\ 141\ 79(30) \times 10^{23}\ \text{mol}^{-1}$.

NOTE 7 The number of defined particles, or elemental entities, of a component in a system divided by the volume of that system is called number concentration.

See Reference [54].

A.3.11
conventional quantity value
conventional value of a quantity
quantity value attributed by agreement to a quantity for a given purpose

EXAMPLE The conventional quantity value of a given mass standard, $m = 100{,}003\ 47$ g.

NOTE 1 The term “conventional true quantity value” is sometimes used for this concept, but its use is discouraged.

NOTE 2 Sometimes a conventional quantity value is an estimate of a true quantity value.

NOTE 3 A conventional quantity value is generally accepted as being associated with a suitably small measurement uncertainty, which might be zero.

[ISO/IEC Guide 99:2007, definition 2.12]

A.3.12
cross-reactivity
degree to which a substance other than the analyte binds to a reagent in a competitive binding immunochemical measurement procedure

EXAMPLES Antibody binding to metabolites of the analyte, structurally similar drugs, etc.

NOTE 1 **Analytical specificity** (A.3.4) is a related concept.

NOTE 2 Cross-reactivity of metabolites can be a desirable attribute of certain examination procedures, such as for screening for the presence of illegal drugs.

NOTE 3 It is important to calculate cross-reactivity on the basis of moles per litre. For guidelines in calculating cross-reactivity, see Reference [70].

NOTE 4 Adapted from Reference [56].

A.3.13
cut-off value
quantity value used as a limit to identify samples that indicate the presence or the absence of a specific disease, condition or measurand

NOTE 1 Measurement results higher than the cut-off value are considered positive and those lower than the cut-off are considered negative.

NOTE 2 Measurement results near the cut-off value can be considered inconclusive.

NOTE 3 The selection of the cut-off value determines the **diagnostic specificity** (A.3.16) and **diagnostic sensitivity** (A.3.15) of the examination.

A.3.14
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 term **analytical sensitivity** (A.3.3) is sometimes used to mean detection limit, but such usage is now discouraged. See A.2.7 and A.2.8 for further information.

NOTE 3 See also **quantitation limit** (A.3.44).

[ISO/IEC Guide 99:2007, definition 4.18]

A.3.15
diagnostic sensitivity
ability of an IVD examination procedure to identify the presence of a target marker associated with a particular disease or condition

NOTE 1 Also defined as percent positivity in samples where the target marker is known to be present. For information regarding description of the diagnostic performance characteristics of an IVD medical device, see Reference [71].

NOTE 2 Diagnostic sensitivity is expressed as a percentage (number fraction multiplied by 100), calculated as 100 × the number of true positive values (TP) divided by the sum of the number of true positive values (TP) plus the number of

false negative values (FP), or 100 × TP/(TP + FN). This calculation is based on a study design where only one sample is taken from each subject.

NOTE 3 The **target condition** (A.3.55) is defined by criteria independent of the examination procedure under consideration.

NOTE 4 Adapted from Reference [69], 4.5.1.

A.3.16
diagnostic specificity
ability of an IVD examination procedure to recognise the absence of a target marker associated with a particular disease or condition

NOTE 1 Also defined as percent negativity in samples where the target marker is known to be absent. For information regarding description of the diagnostic performance characteristics of an IVD medical device, see Reference [71].

NOTE 2 Diagnostic specificity is expressed as a percentage (number fraction multiplied by 100), calculated as 100 × the number of true negative values (TN) divided by the sum of the number of true negative plus the number of false positive (FP) values, or 100 × TN/(TN + FP). This calculation is based on a study design where only one sample is taken from each subject.

NOTE 3 The **target condition** (A.3.55) is defined by criteria independent of the examination procedure under consideration.

NOTE 4 Adapted from Reference [69], 4.5.1.

A.3.17
high dose hook effect
negative bias in an immunochemical measurement procedure caused by impairment of antigen-antibody cross-linking when the antigen concentration is in excess relative to the antibody concentration or when the antibody concentration is in excess relative to the antigen concentration

NOTE 1 Sometimes called the prozone phenomenon.

NOTE 2 Adapted from Reference [72].

A.3.18
influence quantity
quantity that, in a direct measurement, does not affect the quantity that is actually measured, but affects the relation between the indication and the measurement result

EXAMPLES

— Concentration of bilirubin in a direct measurement of haemoglobin concentration in human blood plasma;

— background pressure in the ion source of a mass spectrometer during a measurement of amount-of-substance fraction.

NOTE 1 An indirect measurement involves a combination of direct measurements, each of which can be affected by influence quantities.

NOTE 2 In the GUM, the concept influence quantity is defined as in the previous edition of the VIM, covering not only the quantities affecting the measuring system, as in the definition above, but also those quantities that affect the quantities actually measured. Also, in the GUM this concept is not restricted to direct measurements.

[ISO/IEC Guide 99:2007, definition 2.52]

A.3.19
interfering quantity
interferent
quantity that is not the measurand but that affects the result of the measurement

EXAMPLES

— Effect of bilirubin, haemoglobin, lipids or coloured drugs on certain colorimetric measurement procedures;

— cross-reacting metabolites in an immunochemical measurement procedure (see **cross-reactivity**, A.3.12).

NOTE 1 An interfering quantity can be an influence quantity, but is not limited to direct measurements. See also **analytical interference** (A.3.2).

NOTE 2 Derived in part from the definition of **influence quantity** (A.3.18).

A.3.20
intermediate measurement precision
intermediate precision
measurement precision under a set of conditions of measurement that includes the same measurement procedure, same location and replicate measurements on the same or similar objects over an extended period of time, but can include other conditions involving changes

NOTE 1 The conditions changed and unchanged should be specified to a practical extent, particularly variables such as calibrations, reagent lots, measuring systems, operators and environmental conditions.

NOTE 2 In evaluating IVD medical devices, the intermediate precision conditions are generally selected to represent the actual use conditions of the IVD medical device over an extended period of time.

NOTE 3 Relevant statistical terms are given in ISO 5725-3[6].

NOTE 4 Intermediate precision can be expressed quantitatively in terms of the dispersion characteristics of the results, such as standard deviation, variance and coefficient of variation.

NOTE 5 Adapted from ISO/IEC Guide 99:2007, definitions 2.22 and 2.23.

A.3.21
linearity of a measuring system
linearity
ability to provide measured quantity values that are directly proportional to the value of the measurand in the sample

NOTE 1 For IVD medical devices, linearity pertains to measurement results within a given **measuring interval** (3.46) after correction or linearization of the **measurement indications** (A.3.28).

NOTE 2 Linearity is evaluated by measuring samples containing measurands that are known by formulation or known relative to each other (not necessarily known absolutely). When the measurement results are plotted against the absolute or relative measurand values, the degree to which the plotted curve conforms to a straight line is a measure of linearity.

NOTE 3 Adapted from References [67] and [73].

A.3.22
material measure
measuring instrument reproducing or supplying, in a permanent manner during its use, quantities of one or more given kinds, each with an assigned value

EXAMPLES Certified reference material, standard weight, volume measure (supplying one or several quantity values, with or without a quantity value scale).

NOTE The indication of a material measure is its assigned value.

[ISO/IEC Guide 99:2007, definition 3.6]

A.3.23
measured quantity value
measured value
quantity value representing a measurement result

NOTE 1 For a measurement involving replicate measurement indications, each indication can be used to provide a corresponding measured quantity value. This set of individual measured quantity values can be used to calculate a resulting measured quantity value, such as an average or median, usually with a decreased associated measurement uncertainty.

NOTE 2 When the range of the true quantity values believed to represent the measurand is small compared with the measurement uncertainty, a measured quantity value can be considered to be an estimate of an essentially unique true quantity value and is often an average or median of individual measured quantity values obtained through replicate measurements.

NOTE 3 In the case where the range of the true quantity values believed to represent the measurand is not small compared with the measurement uncertainty, a measured value is often an estimate of an average or median of the set of true quantity values.

NOTE 4 In the GUM, the terms “measurement result”, “estimate of the value of the measurand” or just “estimate of the measurand” are used for “measured quantity value”; in laboratory medicine, the term “measurement result” or just “result” is generally used.

[ISO/IEC Guide 99:2007, definition 2.10]

A.3.24
measurement accuracy
accuracy
closeness of agreement between a measured quantity value and a true quantity value of the measurand

NOTE 1 The concept “measurement accuracy” is not a quantity and is not given a numerical quantity value. A measurement is said to be more accurate when it offers a smaller measurement error.

NOTE 2 The term “measurement accuracy” should not be used for measurement trueness and the term “measurement precision” should not be used for measurement accuracy, which, however, is related to both these concepts.

NOTE 3 Measurement accuracy is sometimes understood as closeness of agreement between measured quantity values that are being attributed to a measurand.

[ISO/IEC Guide 99:2007, definition 2.13]

A.3.25
measurement bias
bias
estimate of a systematic measurement error

NOTE 1 Bias is inversely related to trueness.

NOTE 2 An estimation of bias is the average value of a series of measurements minus a **reference quantity value** (A.3.50).

[ISO/IEC Guide 99:2007, definition 2.18]

A.3.26
measurement correction
compensation for an estimated systematic effect

NOTE 1 See ISO/IEC Guide 98-3:2008, 3.2.3, for an explanation of systematic effect.

NOTE 2 The compensation can take different forms, such as an addend or a factor, or can be deduced from a table.

[ISO/IEC Guide 99:2007, definition 2.53]

A.3.27
measurement error
measured quantity value minus a reference quantity value

NOTE 1 The error concept can be used both

— when there is a single reference quantity value to refer to, which occurs if a calibration is made by means of a measurement standard with a measured quantity value having a negligible measurement uncertainty or if a conventional quantity value is given, in which case the measurement error is known and

— if a measurand is supposed to be represented by a unique true quantity value or a set of true quantity values of negligible range, in which case the measurement error is not known.

NOTE 2 Measurement error should not be confused with production error or mistake.

NOTE 3 The sign of the difference must be noted.

[ISO/IEC Guide 99:2007, definition 2.16]

A.3.28
measurement indication
indication
quantity value provided by a measuring instrument or a measuring system

NOTE 1 A measurement indication can be presented in visual or acoustic form or can be transferred to another device. A measurement indication is often given by the position on the display for analogue outputs, a displayed or printed number for digital outputs, a code pattern for code outputs, or an assigned quantity value for material measures.

NOTE 2 A measurement indication and a corresponding value of the quantity being measured are not necessarily values of quantities of the same kind.

NOTE 3 The value read from an instrument display is called the direct indication; it can be multiplied by an instrument constant to give the measurement indication.

NOTE 4 The quantity can be the measurand, a measurement signal or another quantity to be used in calculating the **measurement result** (3.45).

[ISO/IEC Guide 99:2007, definition 4.1]

A.3.29
measurement precision
precision
closeness of agreement between measurement indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions

NOTE 1 Measurement precision is usually expressed numerically by measures of imprecision, such as standard deviation, variance or coefficient of variation under the specified conditions of measurement.

NOTE 2 The specified conditions can be, for example, repeatability conditions of measurement, intermediate precision conditions of measurement, or reproducibility conditions of measurement (see ISO 5725-5[78]).

NOTE 3 Measurement precision is used to define measurement repeatability, intermediate measurement precision, and measurement reproducibility.

NOTE 4 Replicate measurements means measurements that are obtained in a manner not influenced by a previous measurement on the same or similar sample.

[ISO/IEC Guide 99:2007, definition 2.15]

A.3.30
measurement repeatability
repeatability
measurement precision under a set of conditions of measurement that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time

NOTE 1 In clinical chemistry, the term within-run precision or intra-series precision is sometimes used to designate this concept.

NOTE 2 In evaluating an IVD medical device, repeatability conditions are generally selected to represent essentially unchanged conditions (called repeatability conditions) resulting in the minimum variability of measurement results. Repeatability information can be useful for troubleshooting purposes.

NOTE 3 Repeatability can be expressed quantitatively in terms of the dispersion characteristics of the results, such as repeatability standard deviation, repeatability variance and repeatability coefficient of variation. Relevant statistical terms are given in ISO 5725-2[77].

NOTE 4 Adapted from ISO/IEC Guide 99:2007, definitions 2.20 and 2.21.

A.3.31
measurement reproducibility
reproducibility
measurement precision under conditions of measurement that include different locations, operators, measuring systems, and replicate measurements on the same or similar objects

NOTE 1 In clinical chemistry, the term laboratory-to-laboratory precision is sometimes used to designate this concept.

NOTE 2 In evaluating an IVD medical device, reproducibility conditions are generally selected to represent maximally changed conditions (called reproducibility conditions) resulting in the variability of measurement results that would be encountered when comparing results among independent laboratories, such as would occur in inter-laboratory comparison programmes (e.g., proficiency testing, external quality assurance or laboratory standardization trials).

NOTE 3 Reproducibility can be expressed quantitatively in terms of the dispersion characteristics of the results, such as reproducibility standard deviation, reproducibility variance and reproducibility coefficient of variation. Relevant statistical terms are given in ISO 5725-2[77].

NOTE 4 The different measuring systems can use different measurement procedures.

NOTE 5 A specification should give the conditions changed and unchanged, to the extent practical.

NOTE 6 Adapted from ISO/IEC Guide 99:2007, definitions 2.24 and 2.25.

A.3.32
measurement signal
signal
quantity that represents the measurand and which is functionally related to it

NOTE A measurement signal can be a **measurement indication** (A.3.28).

See ISO Guide 30[25].

A.3.33
measurement standard
realization of the definition of a given quantity, with stated quantity value and associated measurement uncertainty, used as a reference

EXAMPLE 1 1 kg mass measurement standard with an associated standard measurement uncertainty of 3 µg.

EXAMPLE 2 Hydrogen reference electrode with an assigned quantity value of 7,072 and an associated standard measurement uncertainty of 0,006.

EXAMPLE 3 Set of reference solutions of cortisol in human serum having a certified quantity value with measurement uncertainty for each solution.

EXAMPLE 4 Reference material providing quantity values with measurement uncertainties for the mass concentration of each of ten different proteins.

NOTE 1 A measurement standard is frequently used as a reference in establishing measured quantity values and associated measurement uncertainties for other quantities of the same kind, thereby establishing metrological traceability through calibration of other measurement standards, measuring instruments or measuring systems.

NOTE 2 A realization of the definition of a given quantity can be provided by a measuring system, a material measure, or a reference material.

NOTE 3 The term realization is used here in the most general meaning. It denotes three procedures of realization. The first one consists in the physical realization of the measurement unit from its definition and is realization *sensu stricto*. The second, termed reproduction, consists not in realizing the measurement unit from its definition but in setting up a highly reproducible measurement standard based on a physical phenomenon. The third procedure consists of adopting a material measure as a measurement standard, such as in the case of the measurement standard of 1 kg.

NOTE 4 The word embodiment is sometimes used in the English language instead of realization.

NOTE 5 The hierarchy of measurement standards includes primary measurement standards – whose quantity values and measurement uncertainties are established using primary measurement procedures or created as an artefact, chosen by convention, and secondary measurement standards – whose quantity values and measurement uncertainties are assigned through calibration with respect to a primary measurement standard for a quantity of the same kind. The relation can be obtained directly between a primary measurement standard and a secondary measurement standard, or involve an intermediate measuring system calibrated by the primary measurement standard and assigning a measurement result to the secondary measurement standard. See ISO/IEC Guide 99:2007, 5.4 and 5.5.

EXAMPLE 5 Primary measurement standard of amount-of-substance concentration prepared by dissolving a known amount of substance of a chemical component to a known volume of solution.

NOTE 6 A measurement standard recognised by signatories to an international agreement and intended to serve worldwide is called an international measurement standard, such as “chorionic gonadotropin, World Health Organization (WHO) 4th International Standard 1999, 75/589, 650 International Units per ampoule”. A measurement standard recognised by a national authority to serve in the country is called a national measurement standard (see ISO/IEC Guide 99:2007, 5.2).

NOTE 7 A measurement standard designated for the calibration of working measurement standards for quantities of a given kind in a given organization or at a given location is called a reference measurement standard (see ISO/IEC Guide 99:2007, 5.6). A measurement standard that is used routinely to calibrate or verify measuring instruments or measuring systems is called a working measurement standard (see ISO/IEC Guide 99:2007, 5.7.). A working measurement standard is usually calibrated with respect to a reference measurement standard.

NOTE 8 A standard measurement uncertainty associated with a measurement standard is always a component of the combined standard measurement uncertainty (see ISO/IEC Guide 98-3:2008, 2.3.4) in a measurement result obtained using the measurement standard. Frequently, this component is small compared with other components of the combined standard measurement uncertainty.

NOTE 9 Quantity value and measurement uncertainty must be determined at the time when the measurement standard is used.

[ISO/IEC Guide 99:2007, definition 5.1]

A.3.34
measurement trueness
trueness
closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value

NOTE 1 Measurement trueness is not a quantity and thus cannot be expressed numerically, but measures for closeness of agreement are given in ISO 5725-3.

NOTE 2 Measurement trueness is inversely related to **systematic measurement error** (A.3.54), but is not related to **random measurement error** (A.3.48).

NOTE 3 The term **measurement accuracy** (A.3.24) should not be used for measurement trueness and vice versa.

[ISO/IEC Guide 99:2007, definition 2.14]

A.3.35
measurement uncertainty
uncertainty of measurement
non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used

NOTE 1 Measurement uncertainty includes components arising from systematic effects, such as components associated with corrections and the assigned quantity values of measurement standards, as well as the definitional uncertainty. Sometimes estimated systematic effects are not corrected for but instead associated measurement uncertainty components are incorporated.

NOTE 2 The parameter cannot be negative. The parameter might be, for example, a standard deviation called standard measurement uncertainty (or a specified multiple of it), or the half-width of an interval, having a stated coverage probability.

NOTE 3 The standard measurement uncertainty that is obtained from the measurement results of the input quantities in a measurement model is called combined standard measurement uncertainty. The product of a combined standard measurement uncertainty and a coverage factor larger than the number one is called the expanded measurement uncertainty in ISO/IEC Guide 99:2007, 2.35, overall uncertainty by the BIPM Working Group on the Statement of Uncertainties, and simply uncertainty in IEC documents.

NOTE 4 The minimum measurement uncertainty resulting from the finite amount of detail in the definition of a measurand is called “definitional uncertainty” in ISO/IEC Guide 99:2007, 2.27. In the GUM and in IEC 60359[83], the concept is called intrinsic uncertainty.

NOTE 5 Measurement uncertainty comprises, in general, many components. Some of these can be evaluated by Type A evaluation of measurement uncertainty from the statistical distribution of the quantity values from series of measurements and can be characterized by standard deviations. The other components, which can be evaluated by Type B evaluation of measurement uncertainty, can also be characterized by standard deviations, evaluated from probability density functions based on experience or other information (see ISO/IEC Guide 99:2007, 2.26, Note 3).

NOTE 6 The statement of a measurement uncertainty, of the components of that measurement uncertainty, and of their calculation and combination is called an uncertainty budget. An uncertainty budget typically includes the measurement model, estimates and measurement uncertainties of the quantities in the measurement model, covariances, type of applied probability density functions, degrees of freedom, type of evaluation of measurement uncertainty, and any coverage factor (see ISO/IEC Guide 99:2007, 2.33).

NOTE 7 In general, for a given set of information, it is understood that the measurement uncertainty is associated with a stated quantity value attributed to the measurand. A modification of this value results in a modification of the associated uncertainty.

[ISO/IEC Guide 99:2007, definition 2.26]

A.3.36
measurement unit
unit of measure
real scalar quantity, defined and adopted by convention, with which any other quantity of the same kind can be compared to express the ratio of the two quantities as a number

NOTE 1 Measurement units are designated by conventionally assigned names and symbols (see References [23] and [54]).

NOTE 2 For a given quantity, the short term unit is often combined with the quantity name, such as mass unit or unit of mass.

NOTE 3 Measurement units of quantities of dimension one are numbers. In some cases these measurement units are given special names, e.g. radian, steradian and decibel, or are expressed by quotients such as millimole per mole equal to 10^{-3} and microgram per kilogram equal to 10^{-9}.

[ISO/IEC Guide 99:2007, definition 1.9]

A.3.37
measuring system
set of one or more measuring instruments and often other devices, including any reagent and supply, assembled and adapted to give measured quantity values within specified intervals for quantities of specified kinds

NOTE A measuring system can consist of only one device used for making measurements, which can either be an indicating measuring instrument or a material measure, and which can be used alone or in conjunction with supplementary devices (see ISO/IEC Guide 99:2007, 3.1).

[ISO/IEC Guide 99:2007, definition 3.2]

A.3.38
metrological comparability of measurement results
comparability of measurement results, for quantities of a given kind, that are metrologically traceable to the same reference

EXAMPLE Measurement results from two different commercial clinical chemistry measuring systems are comparable when they are both metrologically traceable to the same primary reference standard, for example, a Certified Reference Material for the mass concentration of glucose.

NOTE 1 For this definition, a reference can be a definition of a measurement unit through its practical realization, or a **measurement procedure** (3.44) including the measurement unit for a non-ordinal quantity, or a **measurement standard** (A.3.33).

NOTE 2 Metrological comparability of measurement results does not necessitate that the measured quantity values and associated measurement uncertainties compared are of the same order of magnitude.

[ISO/IEC Guide 99:2007, definition 2.46]

A.3.39
metrological compatibility of measurement results
property of a set of measurement results for a specified measurand, such that the absolute value of the difference of any pair of measured quantity values from two different measurement results is smaller than some chosen multiple of the standard measurement uncertainty of that difference

NOTE 1 Metrological compatibility of measurement results replaces the traditional concept of staying within the error, as it represents the criterion for deciding whether two measurement results refer to the same measurand or not. If in a set of measurements of a measurand, thought to be constant, a measurement result is not compatible with the others, either the measurement was not correct (e.g. its measurement uncertainty was assessed as being too small) or the measured quantity changed between measurements.