International Standard

ISO 5649

First edition
2024-11

Medical laboratories — Concepts and specifications for the design, development, implementation and use of laboratory-developed tests

Laboratoires médicaux — Concepts et spécifications relatifs à la conception, au développement, à la mise en œuvre et à l'utilisation des tests développés en laboratoire

Reference number
ISO 5649:2024(en)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

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

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Medical laboratory testing is carried out to an appropriate standard and all work is performed with a high level of skill and competence so as not to produce unreliable results which can lead to patient harm.

In many medical laboratories, the majority of routine clinical samples are processed and analysed using commercially available tests on automated instrumentation purchased from various manufacturers of in vitro diagnostic (IVD) medical devices. The marketing of medical devices is usually regulated by national bodies, and devices must undergo stringent assessment before they can be placed on the market and put into service.

However, there are clinical indications for which there are no commercially available IVD medical devices for the specific intended use or there is a requirement for adding additional specification/approach(es) to a commercial IVD medical device. Such tests are referred to as laboratory-developed tests (LDTs). LDTs can be defined as tests developed (or modified) and used within a laboratory to carry out testing on specimens, such as blood, body fluids and tissues, and samples derived from human specimens, such as bacterial isolates, where the results are intended to assist in clinical diagnosis or be used in making decisions concerning clinical management.

Due to technological development, advanced examinations are continuously introduced in the medical laboratory. These can include, but are not limited to liquid chromatography-tandem mass spectrometry (LC-MS/MS), time-of-flight/mass spectrometry (TOF/MS), nuclear magnetic resonance (NMR), molecular diagnostic testing (e.g. polymerase chain reaction (PCR) based and next generation sequencing (NGS)), in situ hybridization (ISH), immunohistochemistry (IHC), whole slide scanning and imaging, algorithm-based analyses and other emerging technologies. These techniques may be developed in a clinical research laboratory, transferred to the medical laboratory, and placed into routine use as diagnostic tests without going through the same standard approval processes as commercially available IVD medical devices. These tests are also considered to be LDTs.

LDTs have become more complex because of available technology and are increasingly being used to diagnose high-risk conditions such as cancer, genetic disorders, rare diseases, etc., which in turn highlights the need to ensure that the results obtained are accurate and reproducible to safeguard the health and well-being of patients. While many laboratories can perform validation studies of these tests, there is currently no international standard by which to assess the rationale for their intended use, design, development, performance, quality, and reliability.

This document is intended to be used to provide additional guidance to laboratories using LDTs. Accreditation to ISO 15189 is not a pre-requisite for laboratories to use this document.

Conceptually, the lifecycle of an LDT involves sequential phases that extend from the feasibility assessment to the final retirement of the examination procedure. The main phases of a typical LDT lifecycle described in this document, therefore, include the feasibility assessment, the design and development phase, the preliminary/pilot testing followed by the performance evaluation phase, including validation and the verification phases, the monitoring and review activities during LDT use, and the final retirement of the LDT. The illustration shown in Figure 1 below demonstrates these different phases and indicates which clauses of this document cover the corresponding lifecycle phases for an LDT. The arrows back to previous phases within Figure 1 indicate an iterative, dynamic process which can include look-backs, rework or revalidation for improvement of the LDT.

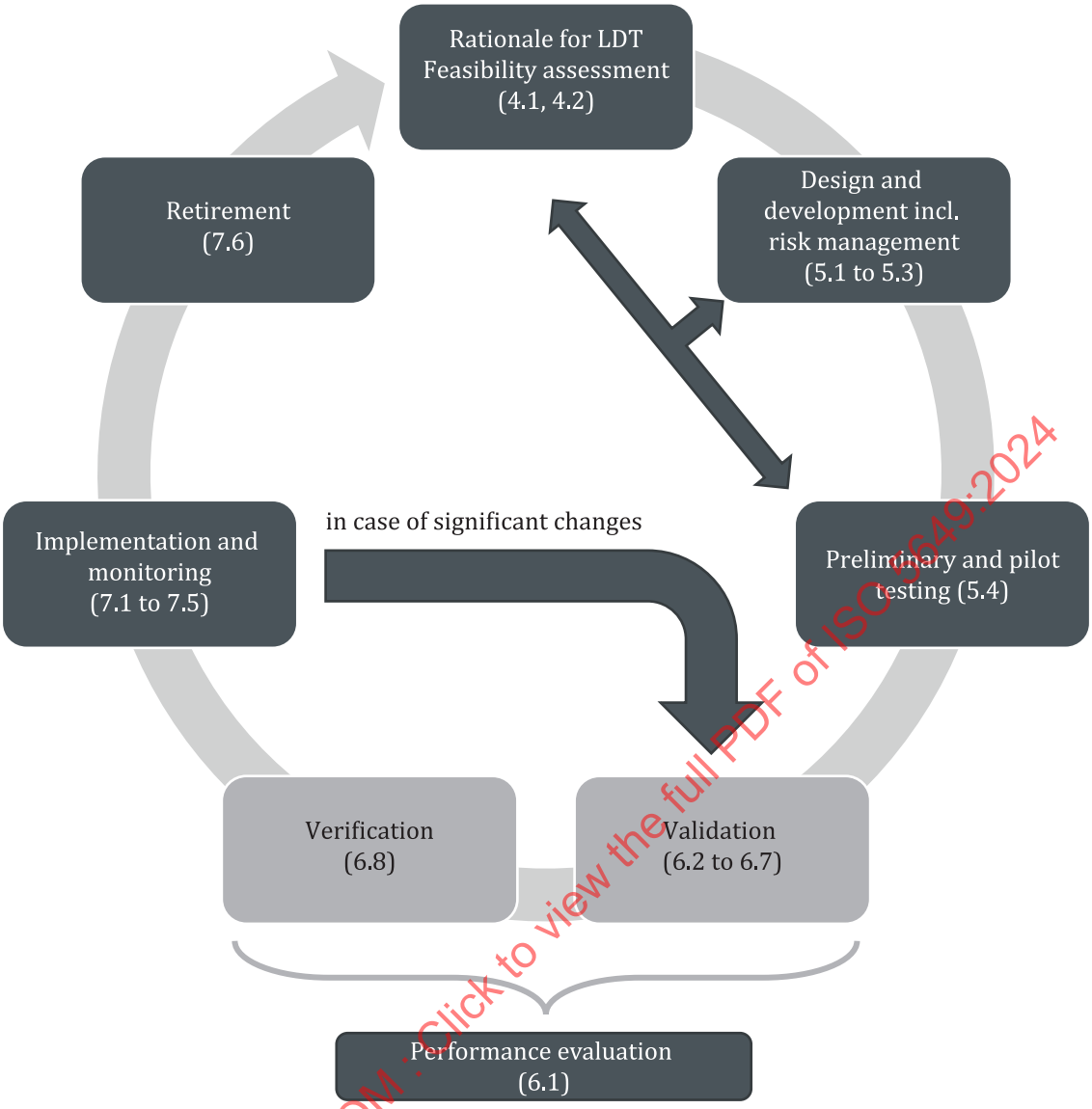

Figure 1 — Possible lifecycle phases of an LDT

The rationale for the use of an LDT and the feasibility assessment consider the demand for an LDT and determine whether analytical and clinical performance of the new LDT can meet requirements for adequate measurement procedure results (refer to 4.1 and 4.2 of this document).

Design and development include the planning and definition of formal specifications for LDT performance including iterative improvement of all LDT components according to the intended use of the LDT. This can include redesign and reassessment of feasibility and the formal specifications of the LDT as a dynamic process covering all aspects of the LDT development (refer to 5.1 to 5.3 of this document).

Preliminary testing precedes the performance evaluation phase and determines the technical aspects of the LDT by demonstrating that the LDT meets the design and development requirements (refer to 5.4 of this document).

Performance evaluation includes the collection, analysis and assessment of performance data typically generated from validation and verification studies, but also includes activities of risk management and supports the demonstration of the conformity of the LDT to applicable principles of safety and performance.

Validation is a defined process to confirm and control that the finally designed and developed LDT is suitable for its intended use and fulfils all analytical and clinical performance claims (refer to 6.2 to 6.7 of this document).

LDT specifications are verified, where relevant aspects of the LDT procedure deviate between the phase of validation and routine use of the LDT (refer to 6.8 of this document for verification).

LDTs are continuously monitored and periodically reviewed to ensure conformity with the original performance specifications. Significant changes of the LDT require a restart of the processes affected by the modification including revalidation (refer to 7.1 to 7.5 of this document for implementation and monitoring).

LDTs that need replacement shall be retired (refer to 7.6 of this document for retirement).

An example for how this lifecycle can be applied to a workflow is presented in Annex A of this document.

Medical laboratories — Concepts and specifications for the design, development, implementation and use of laboratory-developed tests

1 Scope

This document establishes requirements for assuring quality, safety, performance and documentation of laboratory-developed tests (LDTs) as per their intended use for the diagnosis, prognosis, monitoring, prevention or treatment of medical conditions.

It outlines the general principles and assessment criteria by which an LDT shall be designed, developed, characterized, manufactured, validated (analytically and clinically) and monitored for internal use by medical laboratories.

The scope includes regulatory authority approved IVD medical devices that are used in a manner differing from approved labelling or instructions for use for that device (e.g. use of a sample type not included in the intended use, use of instruments or reagents not included in the labelling).

While this document follows a current best practice and state-of-the art approach, it does not provide specific details on how to achieve these requirements within specific disciplines of the medical laboratory nor specific technology platforms.

This document does not specify requirements for examination procedures developed by research or academic laboratories developing and using testing systems for non-IVD purposes. However, the concepts presented in this document can also be useful for these laboratories.

This document does not apply to the design, development and industrial production of commercially used IVD medical devices.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
analyte
component represented in the name of a measurable quantity

EXAMPLE In “mass of protein in 24-hour urine”, “protein” is the analyte. In “amount of substance of glucose in plasma”, “glucose” is the analyte. In both cases, the long phrase represents the *measurand* (3.28)

[SOURCE: ISO 17511:2020, 3.1]

3.2
analytical performance
analytical performance of an LDT
ability of a *laboratory-developed test (LDT)* (3.25) to detect or measure a particular *analyte* (3.1)

Note 1 to entry: *Clinical evidence* (3.7) of an LDT is composed of three elements: *scientific validity* (3.51), analytical performance and *clinical performance* (3.8).

[SOURCE: IMDRF/GRRP WG/N47:2018, 3.2[20], modified — "IVD medical device" was replaced by "LDT".]

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 to entry: The analytical sensitivity can depend on the value of the quantity being measured.

Note 2 to entry: The change considered in the value of the quantity being measured shall be large compared with the resolution.

Note 3 to entry: The analytical sensitivity of a measuring system is the slope of the calibration curve.

Note 4 to entry: Analytical sensitivity should not be used to mean *detection limit* (3.13) or *quantitation limit* (3.43) and should not be confused with *diagnostic sensitivity* (3.15).

[SOURCE: ISO 18113-1:2022, 3.2.4]

3.4
analytical specificity
selectivity of a measurement procedure
capability of a measuring system, using a specified *measurement procedure* (3.31), to provide measurement results for one or more *measurands* (3.28) 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 to entry: Lack of analytical specificity is called analytical interference.

Note 2 to entry: Lack of analytical specificity in immunochemistry measurement procedures can be due to *cross-reactivity* (3.11).

Note 3 to entry: Specificity of a measurement procedure should not be confused with *diagnostic specificity* (3.16).

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

[SOURCE: ISO 18113-1:2022, 3.2.5]

3.5
bias
measurement bias
estimate of a systematic measurement error

Note 1 to entry: See also ISO/IEC Guide 99:2007, 2.17, systematic measurement error.

Note 2 to entry: This definition applies to quantitative measurements only.

[SOURCE: ISO 15189:2022, 3.1, modified — a new Note 1 to entry was added and former Note 1 to entry is Note 2 to entry.]

3.6
biological reference interval
reference interval
specified interval of the distribution of values taken from a biological reference population

Note 1 to entry: A biological reference interval is commonly defined as the central 95 % interval. Another size or an asymmetrical location of the biological reference interval can be more appropriate in particular cases.

Note 2 to entry: A biological reference interval can depend upon the type of primary sample and the *examination* (3.17) procedure used.

Note 3 to entry: 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 to entry: Terms such as 'normal range', 'normal values', and 'clinical range' are ambiguous and therefore discouraged.

[SOURCE: ISO 15189:2022, 3.2]

3.7
clinical evidence
information that supports the *clinical utility* (3.9) of a *laboratory-developed test (LDT)* (3.25) for its *intended use* (3.22), including *scientific validity* (3.51), *analytical performance* (3.2), and *clinical performance* (3.8)

3.8
clinical performance
clinical performance of a laboratory-developed test (LDT)
ability of a *laboratory-developed test (LDT)* (3.25) to yield results that are correlated with a particular clinical condition/physiological state in accordance with target population and intended user

Note 1 to entry: Clinical performance can include *diagnostic sensitivity* (3.15) and *diagnostic specificity* (3.16) based on the known clinical or physiological state of the individual, and *negative predictive values* (3.37) and *positive predictive values* (3.42) based on the prevalence of the disease.

Note 2 to entry: The clinical performance of an LDT is also referred to as the ability of a test to discriminate between the target condition and health.

[SOURCE: IMDRF/GRRP WG/N47:2018, 3.11[20], modified — "IVD Medical Device" was replaced by "LDT" and Note 2 was replaced.]

3.9
clinical utility
usefulness of the results obtained from testing and the value of the information to either the individual being tested or the broader population, or both

Note 1 to entry: Aside from *scientific validity* (3.51), *analytical performance* (3.2), and *clinical performance* (3.8), a laboratory is not required to demonstrate any other elements of the clinical utility of a *laboratory-developed test (LDT)* (3.25).

Note 2 to entry: Adapted from GHTF/SG5/N6:2012, 4.7[23].

3.10
competence
demonstrated ability to apply knowledge and skills to achieve intended results

[SOURCE: ISO 15189:2022, 3.5]

3.11
cross-reactivity
degree to which a substance other than the *analyte* (3.1) intended to be measured affects an *examination* (3.17) procedure

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

Note 1 to entry: *Analytical specificity* (3.4) is a related concept.

Note 2 to entry: 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 to entry: It is important to calculate cross-reactivity on the basis of moles per litre. For guidelines in calculating cross-reactivity, see Reference [54].

[SOURCE: ISO 18113-1:2022, 3.2.14, modified — "binds to a reagent in a competitive binding immunochemical measurement procedure" was replaced by "intended to be measured affects an examination procedure".]

3.12
design and manufacture
activities that may include specification development, production, assembly, processing, sterilization, installation of a *laboratory-developed test (LDT)* (3.25) or putting a collection of devices, and possibly other products, together for a medical purpose as specified by the laboratory

[SOURCE: IMDRF/GRRP WG/N47:2018, 3.25[20] NOTE 3, modified — "medical device" was replaced by "LDT".]

3.13
detection limit
limit of detection
measured quantity value, obtained by a given *measurement procedure* (3.31), 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 to entry: IUPAC recommends default values for α and β equal to 0,05.

Note 2 to entry: The abbreviation LoD is sometimes used.

Note 3 to entry: The term "sensitivity" is discouraged for 'detection limit'.

[SOURCE: JCGM 200:2012, 4.18[19]]

3.14
diagnostic accuracy
extent of agreement between the information from the test under evaluation and applicable performance attributes as measured by a reference method

Note 1 to entry: Diagnostic accuracy can be expressed in different ways, including sensitivity-specificity pairs, likelihood ratio pairs, and the area under a receiver operating characteristic curve.

Note 2 to entry: Diagnostic accuracy shall be interpreted in context with the condition of interest and the combination of specific criteria and methods used.

Note 3 to entry: Diagnostic accuracy is not the same as *measurement accuracy* (3.29), which is the closeness of a single result of a measurement and a true value.

[SOURCE: CLSI Harmonized Terminology Database,[49] Project: EP12, M55, modified — "diagnostic accuracy criteria" has been replaced by "applicable performance attributes as measured by a reference method".]

3.15
diagnostic sensitivity
ability of an *examination* (3.17) procedure to have positive results associated with a particular disease or condition

Note 1 to entry: 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* (3.39) of a *laboratory-developed test (LDT)* (3.25), see Reference [55].

Note 2 to entry: 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 (FN), or 100 × TP / (TP + FN). This calculation is based on a study design where only one sample is taken from each subject.

Note 3 to entry: The target condition is defined by criteria independent of the examination procedure under consideration.

[SOURCE: ISO 18113-1:2022, 3.2.17]

3.16
diagnostic specificity
ability of an *examination* (3.17) procedure to have negative results associated with an absence of a particular disease or condition

Note 1 to entry: 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* (3.39) of a *laboratory-developed test (LDT)* (3.25), see Reference [55].

Note 2 to entry: 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 to entry: The target condition is defined by criteria independent of the examination procedure under consideration.

[SOURCE: ISO 18113-1:2022, 3.2.18]

3.17
examination
set of operations having the objective of determining the numerical value, text value or characteristics of a property

Note 1 to entry: An examination may be the total of a number of activities, observations or measurements required to determine a value or characteristic.

Note 2 to entry: Laboratory examinations that determine a numerical value of a property are called “quantitative examinations”; those that determine the characteristics of a property are called “qualitative examinations”.

Note 3 to entry: Laboratory examinations are also called “assays” or “tests”.

[SOURCE: ISO 15189:2022, 3.8]

3.18
expected service life
expected lifetime
service life
time period specified by the laboratory during which the *laboratory-developed test (LDT)* (3.25) is expected to maintain safe and effective use

Note 1 to entry: The expected service life can be determined by *stability* (3.54).

Note 2 to entry: Maintenance, repairs, or upgrades, e.g. *safety* (3.50) or cybersecurity modifications, can be necessary during the expected service life.

[SOURCE: IMDRF/GRRP WG/N47:2018, 3.13,[20], modified — “manufacturer” was replaced by “laboratory” and “medical device or IVD medical device” was replaced by “LDT”.]

3.19
expiry date
expiration date
upper limit of the time interval during which the *performance characteristics* (3.39) of a material stored under specified conditions can be assured

Note 1 to entry: Expiry dates are assigned to reagents, calibrators, control materials, and other components by the laboratory, based on experimentally determined *stability* (3.54) properties.

Note 2 to entry: Guidelines for determining the stability are found in ISO 23640:2011.

[SOURCE: ISO 18113-1:2022, 3.1.22, modified — in Note 1 to entry, “manufacturer” was replaced by “laboratory”.]

3.20
feasibility assessment
initial part of the *laboratory-developed test (LDT)* (3.25) *lifecycle* (3.26) phases that includes consideration of a potential *examination* (3.17) method, by the laboratory, concerning various issues that are relevant to the decision of developing a new examination method (e.g. *laboratory users’* (3.24) needs and expectations and availability of scientific data)

Note 1 to entry: Adapted from CLSI EP 19[43].

3.21
indications for use
general description of the disease or condition that the *laboratory-developed test (LDT)* (3.25) diagnoses, helps prevent, or monitors, including a description of the patient population for which the LDT is intended

[SOURCE: IMDRF/GRRP WG/N47, 3.17[20], modified — “medical device or IVD medical device” was replaced by “LDT”.]

3.22
intended use
intended purpose
objective intent regarding the use of a product, process or service as reflected in the specifications, instructions and information regarding the *laboratory-developed test (LDT)* (3.25) provided by the laboratory

Note 1 to entry: The intended use can include the *indications for use* (3.21).

[SOURCE: IMDRF/GRRP WG/N47:2018, 3.13,[20], modified — “regarding the LDT” was added, “manufacturer” was replaced by “laboratory”.]

3.23
in vitro diagnostic medical device
IVD medical device
medical device, whether used alone or in combination, intended for the in vitro *examination* (3.17) of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes

Note 1 to entry: IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological state.

Note 2 to entry: In some jurisdictions, certain IVD medical devices can be covered by other regulations.

[SOURCE: IMDRF/GRRP WG/N52, 3.18[21], modified — “by the manufacturer” was deleted.]

3.24
laboratory user
individual or entity requesting services of the medical laboratory

Note 1 to entry: Users can include patients, clinicians, and other laboratories or institutions that send samples for *examination* (3.17).

[SOURCE: ISO 15189:2022, 3.16]

3.25
laboratory-developed test
LDT
laboratory-developed examination
in-house IVD
laboratory designed or developed method
test or *examination* (3.17) which is designed, developed, manufactured (or modified) and used within a single laboratory or laboratory network to carry out testing on samples, where the results are intended to assist in clinical diagnosis or be used in making decisions concerning clinical management

Note 1 to entry: There are four broad situations, as follows, where a laboratory is considered to have developed an LDT:

a) LDTs developed from first principles (de novo): this situation applies when a laboratory or laboratory network is responsible for the design and production of the examination.

b) LDTs developed or modified from a published or any other source: these include tests produced by a laboratory

   1) in accordance with scientific literature;

   2) from the design specifications of an LDT manufactured by another laboratory; or

   3) from the design specifications of any other source.

c) LDTs developed as assembly or combination of commercially authorized *in vitro diagnostic medical devices* (3.23) and other, non-IVD products to a novel system for IVD purposes.

d) LDTs used for a purpose other than the *intended use* (3.22) assigned by the commercial manufacturer: IVD medical devices become a laboratory-developed test (LDT) when

   1) the intended use is different than the intended use claimed by the commercial manufacturer, for example when a “laboratory product” (“for research use only”-product, “for laboratory use only”-product, etc.) is used by the laboratory for IVD purposes;

   2) a physical component of the commercial IVD medical device is modified, substituted, or removed; or

   3) the test is not used in accordance with the manufacturer’s instructions for use, including *significant changes* (3.53) of the intended use of the IVD medical device, such as, for example, the addition or change of specimen type(s).

3.26
lifecycle
phases in the life of a *laboratory-developed test (LDT)* (3.25), from the initial *feasibility assessment* (3.20) to final retirement

[SOURCE: IMDRF/GRRP WG/N47:2018, 3.24,[20] modified — “medical device” was replaced by “LDT”.]

3.27
linearity
linearity of a measuring system
ability, within a given *measuring interval* (3.35), to provide results that are directly proportional to the concentration (or amount) of the *measurand* (3.28) in the sample

Note 1 to entry: Linearity typically refers to overall system response (i.e. the final analytical answer rather than the raw instrument output).

Note 2 to entry: The linearity of a system is measured by testing levels of a measurand that are known by formulation or known relative to each other (not necessarily known absolutely).

Note 3 to entry: For some applications, users may choose to verify linearity using a linear equation that includes a term for the y-intercept. In this less restrictive case, linearity is the ability of a testing system to provide results that conform to a straight line of the form Y = AX + B within a given measuring interval. Additional information, e.g. from a comparison study or calibration *verification* (3.57), should be provided to check whether the term for the y-intercept is close to zero.

Note 4 to entry: Nonlinearity is a contributor to systematic *bias* (3.5). There is no single statistic that can represent an acceptable degree of nonlinearity.

[SOURCE: ISO 18113-1:2022, 3.2.24]

3.28
measurand
quantity intended to be measured

Note 1 to entry: The specification of a measurand requires knowledge of the kind of quantity, description of the state of the phenomenon, body, or substance carrying the quantity, including any relevant component, and the chemical entities involved.

Note 2 to entry: The measurement, including the measuring system and the conditions under which the measurement is carried out, can change the phenomenon, body, or substance such that the quantity being measured can differ from the measurand as defined. In this case, adequate correction is necessary.

EXAMPLE 1 The potential difference between the terminals of a battery can decrease when using a voltmeter with a significant internal conductance to perform the measurement. The open-circuit potential difference can be calculated from the internal resistances of the battery and the voltmeter.

EXAMPLE 2 The length of a steel rod in equilibrium with the ambient temperature of 23 °C will be different from the length at the specified temperature of 20 °C, which is the measurand. In this case, a correction is necessary.

Note 3 to entry: In chemistry, "*analyte* (3.1)", 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.

[SOURCE: JCGM 200:2012, 2.3[19]]

3.29
measurement accuracy
accuracy
accuracy of measurement
closeness of agreement between a measured quantity value and a true quantity value of a *measurand* (3.28)

Note 1 to entry: 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 to entry: The term measurement accuracy should not be used for *measurement trueness* (3.55) and the term *measurement precision* (3.30) should not be used for measurement accuracy, which, however, is related to both these concepts.

Note 3 to entry: Measurement accuracy is sometimes understood as closeness of agreement between measured quantity values that are being attributed to the measurand.

[SOURCE: JCGM 200:2012, 2.13[19]]

3.30
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 to entry: 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 to entry: The specified conditions can be, for example, *measurement repeatability* (3.32), intermediate precision conditions of measurement, or *measurement reproducibility* (3.33).

Note 3 to entry: Measurement precision is used to define measurement repeatability, intermediate measurement precision, and measurement reproducibility.

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

[SOURCE: ISO 18113-1:2022, 3.2.32]

3.31
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 to obtain a measurement result

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

Note 2 to entry: A measurement procedure can include a statement concerning a target *measurement uncertainty* (3.34).

Note 3 to entry: A measurement procedure is sometimes called a standard operating procedure, abbreviated SOP.

[SOURCE: JCGM 200:2012, 2.6[19]]

3.32
measurement repeatability
repeatability
measurement precision (3.30) under a set of conditions of measurement that includes the same *measurement procedure* (3.31), 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 to entry: In clinical chemistry, the term within-run *precision* or intra-series precision is sometimes used to designate this concept.

Note 2 to entry: In evaluating a *laboratory-developed test (LDT)* (3.25), 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 to entry: 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 5725-2:2019.

[SOURCE: ISO 18113-1:2022, 3.2.33, modified — In Note 2 to entry, "IVD medical device" was replaced by "LDT".]

3.33
measurement reproducibility
reproducibility
measurement precision (3.30) under conditions of measurement that include different locations, operators, measuring systems, and replicate measurements on the same or similar objects

Note 1 to entry: In clinical chemistry, the term laboratory-to-laboratory measurement precision is sometimes used to designate this concept.

Note 2 to entry: In evaluating a *laboratory-developed test (LDT)* (3.25), measurement reproducibility conditions are generally selected to represent maximally changed conditions (called measurement 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 to entry: Measurement 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 5725-2:2019.

Note 4 to entry: The different measuring systems can use different *measurement procedures* (3.31).

Note 5 to entry: A specification should give the conditions changed and unchanged, to the extent practical.

[SOURCE: ISO 18113-1:2022, 3.2.34, modified — In Note 2 to entry, "IVD medical device" was replaced by "LDT".]

3.34
measurement uncertainty
MU
non-negative parameter characterizing the dispersion of the quantity values being attributed to a *measurand* (3.28), based on the information used

Note 1 to entry: MU includes components arising from systematic effects, as in the case of corrections to the assigned quantity values of measurement standards. Sometimes estimated systematic effects are not corrected for, but instead, the associated MU components are incorporated.

Note 2 to entry: The parameter may be, for example, a standard deviation (SD) called standard MU (or a specified multiple of it), or the half-width of an interval, having a stated coverage probability.

Note 3 to entry: MU comprises, in general, of many components. Some of these may be evaluated by Type A evaluation of MU from the statistical distribution of the quantity values from series of measurements and can be characterized by SD. The other components, which may be evaluated by Type B evaluation of MU, can also be characterized by SD or evaluated from probability density functions based on experience or other information.

Note 4 to entry: In general, for a given set of information, it is understood that the MU is associated with a stated quantity value attributed to the measurand. A modification of this value may result in a modification of the associated uncertainty.

Note 5 to entry: All measurements have *bias* (3.5) and imprecision. For example, replicate measurements of a sample performed under *repeatability* (3.32) conditions generally produce different values for the same measurand. Because the different values could all be reasonably attributed to the same amount of measurand, there is uncertainty as to which value should be reported as the value of the measurand.

Note 6 to entry: Based on available data about the *analytical performance* (3.2) of a given *measurement procedure* (3.31), an estimation of MU provides an interval of values that is believed to include the actual value of the measurand, with a stated level of confidence.

Note 7 to entry: Available data about the analytical performance of a given measurement procedure typically comprise uncertainty of calibrator assigned values and long-term imprecision of internal quality control materials.

Note 8 to entry: In medical laboratories, most measurements are performed in singleton, and are taken to be an acceptable estimate of the value of the measurand, while the MU interval indicates other values that are also possible.

[SOURCE: ISO 15189:2022, 3.19]

3.35
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 specified conditions

Note 1 to entry: The measuring interval over which the *performance characteristics* (3.39) of a *laboratory-developed test (LDT)* (3.25) have been validated has been called the reportable range.

Note 2 to entry: The lower limit of a measurement interval should not be confused with the *detection limit* (3.13). See ISO 18113-1:2022, A.2.8 for further information.

Note 3 to entry: For a discussion of the difference between interval and range, see ISO 18113-1:2022, A.2.11.

Note 4 to entry: In molecular diagnostic testing, this may be associated with the *limit of detection (LoD)* (3.13) or *limit of quantitation (LoQ)* (3.43) of the assay.

[SOURCE: ISO 18113-1:2022, 3.1.52, modified — In Note 1 to entry, “IVD medical device” was replaced by “LDT”; Note 4 to entry was added.]

3.36
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* (3.34)

Note 1 to entry: For this definition, a 'reference' can be a definition of a measurement unit through its practical realization, or a *measurement procedure* (3.31) including the measurement unit for a non-ordinal quantity, or a measurement standard.

Note 2 to entry: Metrological traceability requires an established calibration hierarchy.

Note 3 to entry: Specification of the reference shall 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 to entry: For measurements with more than one input quantity in the measurement model, each of the input quantity values should itself be metrologically traceable and the calibration hierarchy involved may form a branched structure or a network. The effort involved in establishing metrological traceability for each input quantity value should be commensurate with its relative contribution to the measurement result.

Note 5 to entry: Metrological traceability of a measurement result does not ensure that the measurement uncertainty is adequate for a given purpose or that there is an absence of mistakes.

Note 6 to entry: A comparison between two measurement standards may 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 7 to entry: 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. The full term of "metrological traceability" is the preferred term used in this document.

[SOURCE: JCGM 200:2012, 2.41[19]]

3.37
negative predictive value
ability of a *laboratory-developed test (LDT)* (3.25) to separate true-negative results from false-negative results for a given attribute in a given population

Note 1 to entry: Negative predictive value (NPV) is calculated as the number of true-negative results (TN) divided by the sum of true-negative and false-negative results (FN) or NPV = TN / (TN + FN).

[SOURCE: GHTF/SG5/N7:2012, 7.2,[24] modified — "device" was replaced by "LDT" and Note 1 to entry was added.]

3.38
performance of a laboratory-developed test (LDT)
performance of an LDT
ability of a *laboratory-developed test (LDT)* (3.25) to achieve its *intended use* (3.22) as claimed by the laboratory

Note 1 to entry: The performance of an LDT consists of the analytical and, where applicable, the clinical performance supporting the intended use of the LDT.

[SOURCE: GHTF/SG5/N6:2012, 4.4,[23] modified — "IVD medical device" was replaced by "LDT" and "manufacturer" was replaced by "laboratory".]

3.39
performance characteristic
metrological property
parameter used to define either the analytical or *clinical performance* (3.8) of a *laboratory-developed test (LDT)* (3.25), or both

EXAMPLE *Diagnostic sensitivity* (3.15), *diagnostic specificity* (3.16), predictive values, *measurement accuracy* (3.29), *measurement reproducibility* (3.33), *measurement repeatability* (3.32), *stability* (3.54), limits of detection and measurement range, earliest clinical detection in comparison with tests of reference.

Note 1 to entry: Information about more than one performance characteristic is usually required to evaluate the suitability of an LDT for its intended medical use.

[SOURCE: ISO 18113-1:2022, 3.1.57, modified — in the definition and in Note 1 to entry, "IVD medical device" was replaced by "LDT".]

3.40
performance evaluation
collection, assessment and analysis of data to establish or verify the analytical and, where applicable, the *clinical performance* (3.8) of a *laboratory-developed test (LDT)* (3.25)

Note 1 to entry: Performance evaluation of an LDT is the comprehensive investigation process by which data are collected, analysed and assessed to demonstrate the performance of the envisioned LDT for the *intended use* (3.22) as established during the design and development phase of the test. Data are typically generated from *validation* (3.56) and *verification* (3.57) studies or obtained from literature reviews that confirm the performance of the LDT. Performance evaluation includes activities of *risk* (3.47) management and supports the demonstration of the conformity of the LDT to the relevant essential principles of *safety* (3.50) and performance.

Note 2 to entry: Validation and verification are included within performance evaluation.

3.41
performance specifications
set of documented requirements to be satisfied by a particular *examination* (3.17) method

Note 1 to entry: For laboratory examinations, *analytical performance* (3.2) characteristics are compared with performance specifications to determine whether the examination method has acceptable performance.

Note 2 to entry: A specification of a *performance characteristic* (3.39) is defined as performance claim (see ISO 18113-1:2022, 3.1.58).

Note 3 to entry: Relevant performance specifications can refer, for example, to the requirements for analytical and *diagnostic sensitivity* (3.15), for the *analytical specificity* (3.4) and *diagnostic specificity* (3.16), for the *robustness* (3.49) of a test system and other requirements.

[SOURCE: CLSI Harmonized Terminology Database,[49] Project: MM17, modified — "method" was replaced by "examination method"; Notes 2 and 3 were added.]

3.42
positive predictive value
ability of a *laboratory-developed test (LDT)* (3.25) to separate true-positive results from false-positive results for a given attribute in a given population

Note 1 to entry: Positive predictive value (PPV) is calculated as the number of true-positive results (TP) divided by the sum of true-positive and false-positive results (FP) or PPV = TP / (TP + FP).

[SOURCE: GHTF/SG5/N7:2012, 7.2,[24], modified — "device" was replaced by "LDT" and Note 1 to entry was added.]

3.43
quantitation limit
limit of quantitation
LoQ
lowest value of *measurand* (3.28) in a sample which can be measured with specified *measurement uncertainty* (3.34), under stated measurement conditions

Note 1 to entry: In IVD labelling, quantitation limit is sometimes referred to as lower limit of determination, lower limit of quantitation, or lower limit of measurement. See ISO 18113-1:2022, A.2.8 for guidelines.

Note 2 to entry: The use of the term "functional sensitivity" to represent this concept is discouraged. See ISO 18113-1:2022, A.2.8 for further information.

[SOURCE: ISO 18113-1:2022, 3.2.49]

3.44
real-world data
data relating to either patient health status or the delivery of health care, or both, which is routinely collected from a variety of sources

Note 1 to entry: Real-world data can come from a number of sources, for example, electronic health records, claims and billing activities, product and disease registries, patient-generated data including in home-use settings, data gathered from other sources that can inform on health status, such as mobile devices.

[SOURCE: US FDA, Real-World Evidence[39]]

3.45
real-world evidence
clinical evidence (3.7) regarding the usage and potential benefits or *risks* (3.47) of a medical product derived from analysis of *real-world data* (3.44)

Note 1 to entry: Real-world evidence can be generated by different study designs or analyses, including, but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (either prospective or retrospective, or both).

[SOURCE: U.S. FDA, Real-World Evidence[39]]

3.46
recovery
measurable increase in *analyte* (3.1) concentration in a sample after adding a known amount of an identical substance

Note 1 to entry: Unspiked and spiked serum specimens are analysed in the assay, and the proportion of the analyte that is detected over pre-existing analyte levels is compared to the amount added. *Accuracy* (3.29) in identifying the amount of analyte added is essential to a recovery study. A recovery of 100 % is considered ideal. An alternative form of recovery studies is called dilution-recovery analysis.

[SOURCE: CLSI Harmonized Terminology Database[49]]

3.47
risk
combination of the probability of occurrence of harm and the severity of that harm

[SOURCE: ISO 14971:2019, 3.18]

3.48
risk control measure
process in which decisions are made and measures implemented by which *risks* (3.47) are reduced to, or maintained within, specified levels

[SOURCE: ISO 18113-1:2022, 3.1.75, modified — Notes to entry were removed.]

3.49
robustness
characteristic of a *laboratory-developed test (LDT)* (3.25) that refers to the degree of tolerability and independence of the performance of its crucial elements to variability in the operator(s), deviations in the properties of the individual constituents, environmental conditions, or the protocol

[SOURCE: CLSI Harmonized Terminology Database[49] Project: I/LA28]

3.50
safety
freedom from unacceptable *risk* (3.47)

[SOURCE: ISO 14971:2019, 3.26]

3.51
scientific validity
association of an *analyte* (3.1) with a clinical condition or a physiological state

Note 1 to entry: Scientific validity is often identified from research and is supported by studies evaluating the analyte for potential clinical applications. Literature review and where applicable, either feasibility or scientific validity studies, or both, performed by the laboratory will help to establish the potential scientific validity.

Note 2 to entry: As the scientific and medical knowledge further develops, the initially established scientific validity can either change or expand, or both, during the *lifecycle* (3.26) of the *laboratory-developed test (LDT)* (3.25).

Note 3 to entry: *Clinical evidence* (3.7) of an LDT is composed of three elements: scientific validity, *analytical performance* (3.2) and *clinical performance* (3.8).

Note 4 to entry: Adapted from GHTF/SG5/N6:2012[23].

3.52
shelf-life
period of time until the *expiry date* (3.19) during which a *laboratory-developed test (LDT)* (3.25) maintains its *stability* (3.54) under the storage conditions specified by the laboratory

Note 1 to entry: Stability and expiry date are related concepts.

Note 2 to entry: Adapted from ISO 18113-1:2022, 3.1.82.

3.53
significant change
change that can reasonably be expected to affect the quality, *safety* (3.50) or *performance characteristics* (3.39) of a *laboratory-developed test (LDT)* (3.25) for its *intended use* (3.22)

Note 1 to entry: A significant change includes a change to any of the following:

— the intended use of the LDT, including any new or extended use, any addition or deletion of a contraindication for the LDT, and any change to the period used to establish its *expiry date* (3.19), any addition or change of specimen type(s), any change of assay type, e.g. from screening assay to confirmatory assay or from qualitative to quantitative assay;

— the manufacturing process, facility, or equipment;

— the manufacturing quality control procedures, including the methods, tests, or procedures used to control the quality, purity, and sterility of the LDT or of the materials used in its manufacture;

— the design of the test, including its performance characteristics, principles of operation, and specifications of materials, energy source, software, or accessories.

Note 2 to entry: Adapted from Health Canada - Guidance Document for the Interpretation of Significant Change of a Medical Device[36] and Medical Device Coordination Group Document MDCG 2022-6: Guidance on significant changes regarding the transitional provision under Article 110(3) of the IVDR, May 2022[29].

3.54
stability
ability of a *laboratory-developed test (LDT)* (3.25) to maintain its *performance characteristics* (3.39) within the limits specified by the laboratory

Note 1 to entry: Stability applies to:

— LDT reagents, calibrators and controls, when stored, transported and used in the conditions specified by the laboratory;

— reconstituted lyophilised materials, working solutions and materials removed from sealed containers, when prepared, used and stored according to the laboratory's operating procedures;

— measuring instruments or measuring systems after calibration.

Note 2 to entry: 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 performance characteristic changes by a stated amount, or

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

[SOURCE: ISO 18113-1:2022, 3.1.85, modified — "IVD medical device" was replaced by "LDT"; "manufacturer" was replaced by "laboratory".]

3.55
trueness
measurement trueness
closeness of agreement between the average of a large number of replicate measured quantity values and a reference quantity value

Note 1 to entry: Trueness is not a quantity and thus cannot be expressed numerically, but measures for closeness of agreement are given in ISO 5725-1.

Note 2 to entry: Trueness is inversely related to systematic measurement error, but it is not related to random measurement error.

Note 3 to entry: *Measurement accuracy* (3.29) should not be used for 'measurement trueness'.

Note 4 to entry: For qualitative *examinations* (3.17), trueness of measurement (closeness of agreement) can be expressed in terms of concordance, i.e. percent agreement with a reference examination.

Note 5 to entry: Trueness is a property of the examination procedure that reflects the *bias* (3.5) of the measurements from the expected or target value. It is described qualitatively as good or bad. An examination procedure has good trueness if the bias of the measurements is low.

[SOURCE: ISO 15189:2022, 3.29]

3.56
validation
confirmation of plausibility for a specific *intended use* (3.22) or application through the provision of objective evidence that specified requirements have been fulfilled

Note 1 to entry: Validation can be applied to claims to confirm the information declared with the claim regarding an intended future use.

Note 2 to entry: Objective evidence can be obtained through observation, measurement, *examination* (3.17) or by other means.

Note 3 to entry: The word "validated" is used to designate the corresponding status.

Note 4 to entry: Specified requirements of an examination method may include the following: *performance specifications* (3.41): *measurement trueness* (3.55), *measurement precision* (3.30) including *measurement repeatability* (3.32), and measurement intermediate precision, *analytical specificity* (3.4), including interfering substances, *detection limit* (3.13) and *quantitation limit* (3.43), *measuring interval* (3.35), clinical relevance, *diagnostic specificity* (3.16) and *diagnostic sensitivity* (3.15).

Note 5 to entry: Validation constitutes an essential part of *performance evaluation* (3.40) of a *laboratory-developed test LDT* (3.25).

Note 6 to entry: For software, "software validation" definition in IEC 62304 and IMDRF/SaMD WG/N23:2015[22] can be used. Software validation confirms that the software fulfils its intended use, e.g. whether the needs of the end users are met.

[SOURCE: ISO 15189:2022, 3.31, modified — Notes 1, 5 and 6 to entry were added.]

3.57
verification
confirmation of truthfulness, through the provision of objective evidence that specified requirements have been fulfilled

EXAMPLE 1 Confirmation that *performance specifications* (3.41) of a measuring system are achieved.

EXAMPLE 2 Confirmation that a target *measurement uncertainty* (3.34) can be met.

Note 1 to entry: Verification can be applied to claims to confirm the information declared with the claim regarding events that have already occurred or results that have already been obtained.

Note 2 to entry: Verification is the process by which the laboratory confirms that the established performance claims of a measuring system (e.g. *trueness* (3.55), *precision* (3.30), reportable range) can be replicated in the laboratory before human sample *examination* (3.17) is performed.

Note 3 to entry: The objective evidence needed for a verification can be the results of an inspection, or other forms of determination, such as performing alternative calculations or reviewing documents.

Note 4 to entry: The word "verified" is used to designate the corresponding status.

Note 5 to entry: Verification of the *analytical performance* (3.2) of *laboratory-developed test (LDT)* (3.25) occurs when certain aspects of the LDT procedure deviate or change between the phases of *validation* (3.56) and routine use of the LDT. Relevant vulnerabilities in the testing procedure should be evaluated during the verification of this deviation/change process.

Note 6 to entry: For software, "software validation" definition in IEC 62304 and IMDRF/SaMD WG/N23:2015[22] can be used. Software verification confirms that the code works for the specific requirements of the code and can include unit tests and integration tests.

[SOURCE: ISO 15189:2022, 3.32, modified — a new Note 1 to entry was added; the original Note 3 to entry was removed; Notes 5 and 6 to entry were added.]

4 General requirements

4.1 Rationale for laboratory-developed tests (LDTs)

The laboratory shall explain a rationale for the use of LDTs established in the laboratory in its documentation.

Relevant elements for the rationale can include:

— absence of commercial tests;

— specific patient needs;

— analytical and clinical device performance characteristics;

— result turn-around times;

— experience from long-term use of examination procedures;

— systems compatibility;

— cost-effectiveness and affordability;

— clinical utility

The extent and detail of the rationale shall be driven by clinical needs and shall be proportionate to the risks of the LDT.

NOTE 1 Refer to 5.2 for more information on risk management and risk differentiation.

NOTE 2 ISO 22367 specifies a process for a medical laboratory to identify and manage the risks to patients, laboratory workers and service providers.

NOTE 3 ISO 14971 specifies terminology, principles, and a process for risk management of medical devices, including software as a medical device and IVD medical devices. The document is intended to assist manufacturers of medical devices to identify the hazards associated with the medical device, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the risk control measures.

NOTE 4 When comparing the cost of an LDT to the cost of a commercial assay, a laboratory can consider the costs of design, development, validation, quality assurance, etc. in addition to the cost of goods.

NOTE 5 The rationale can additionally arise from further considerations (e.g. sustainability, environmental protection).

4.2 Feasibility assessment

Based on the rationale for the establishment of an LDT, the medical laboratory shall perform and document an initial feasibility assessment for the planned LDT.

The feasibility assessment shall consider the following elements, where applicable:

— potential target population for the LDT;

— capabilities of existing measurement procedures;

— expectations for the analytical performance of the planned LDT;

— expectations for the clinical performance of the planned LDT.

NOTE Initial pilot testing (refer to 5.4) can occur during the feasibility assessment.

EXAMPLE The feasibility assessment for the planned LDT can consider: specimen matrices, technology, potential concepts for the design and manufacture, analytical performance, acceptance criteria, overall workflow, labour impact, hands-on time, complexity of testing, specimen processing steps, number of reagents required, testing time, number and type of QC materials, type and volume of sample, clinically actionable results, biological reference intervals, willingness to provide a specimen type, and patient willingness to be tested for a target on a panel versus opting out.

4.3 Management system

4.3.1 General

The laboratory shall have an appropriate management system in place.

The management system shall cover the design and development, manufacturing, performance evaluation, performance review, use and record keeping for the lifecycle of the LDTs established in the laboratory.

NOTE 1 ISO 15189 and ISO/IEC 17025 are examples of recognized standards containing management system requirements (although not stand-alone management system standards). ISO 15189 has been specifically aligned with the requirements for quality and competence of medical laboratories. An example of a recognized quality management system standard is ISO 13485.

NOTE 2 The management system can cover the whole laboratory or just those parts of the laboratory developing and manufacturing LDTs.

NOTE 3 Additional sector-specific management systems can apply.

NOTE 4 ISO 13485 covers the design and development, production, storage and distribution, installation, or servicing of a medical device; ISO 15189 covers quality and competence in medical examination; ISO/TR 20416 describes a proactive and systematic process that manufacturers can use to collect and analyse appropriate data, to provide information for the feedback processes and use this to meet applicable regulatory requirements to gain experience from the post-production activities.

NOTE 5 Regulatory requirements can apply to a management system.

4.3.2 Transfer of laboratory-developed tests (LDTs)

In cases where regulatory requirements allow the transfer of LDTs between laboratories or within a laboratory network, there shall be documented arrangements that define LDT management requirements, responsibilities and liabilities.

Arrangements shall include delivery, receipt and pre-use procedures for transferred LDTs.

NOTE 1 When these LDTs are manufactured and sold by companies or transferred outside the original development laboratory to other distinct laboratories, hospitals or physicians' offices, they require clearance and approval in the large majority of countries by federal or regional agencies as "medical devices". That approval requires clinical validation, verification, and other requirements of premarket notification or approval processes. These devices are usually also required to have regular external quality assurance examinations performed in each laboratory setting, to satisfy requirements of ISO 15189 and ISO/IEC 17025.

NOTE 2 Documentation sharing between original and transfer healthcare organizations can facilitate the transfer process in accordance with applicable regulatory requirements.

NOTE 3 In most jurisdictions, the transfer or exchange of patient samples is not restricted by provisions for the transfer of LDTs.

NOTE 4 Pre-use procedures ensure that the LDT is suitable for the intended use and no significant changes are introduced during the transfer.

4.3.3 Control of subcontractors

Where the laboratory subcontracts parts of the manufacturing process of the device as per the laboratory's instructions, the laboratory shall have documented responsibility and control for the work of the subcontracted party.

The laboratory shall periodically review whether it has sufficiently documented information from the subcontractor's activities potentially influencing relevant safety, quality and performance characteristics of the LDTs established in the laboratory.

NOTE 1 A subcontractor is an individual or a business that enters into a contract to perform part of the manufacturing process with the laboratory manufacturing the LDT. Subcontracting arrangements can include provision of hardware and/or software, manufacture of reagents or consumables and/or even referral of part of the LDT itself, e.g. providing bioinformatics for laboratory-developed molecular testing.

NOTE 2 Control can include specifications for subcontractor quality systems, regular audit, supply chain control and mandatory notification of relevant changes.

5 Requirements for the design and development of laboratory-developed tests (LDTs)

5.1 Determination of LDT performance specifications

5.1.1 General

The medical laboratory shall design and develop formal performance specifications for the planned LDT.

These specifications shall include performance criteria that meet the laboratory user's requirements for the LDT and the acceptance criteria for each requirement.

Initial considerations for the planned LDT shall include the following elements, where applicable:

a) intended use (refer to 5.1.2);

b) scientific validity of the analyte to be measured by the LDT (refer to 5.1.3);

c) specifications for clinical performance (refer to 6.4):

   1) diagnostic specificity;

   2) diagnostic sensitivity;

   3) positive predictive value;

   4) negative predictive value;

d) comparator method such as a reference method;

e) specifications for analytical performance (refer to 6.3);

f) whether the planned LDT produces results that are qualitative, quantitative or semi-quantitative;

g) required quality control procedures;

h) expectations of the stability of test components used for the LDT.

Rationale shall be documented for any of the above items that are determined to not apply as an initial consideration for a planned LDT.

NOTE 1 These parameters define the clinical purpose and usefulness of the planned LDT and will aid in the development of the final test system requirements.

NOTE 2 The initial performance specifications can require modification during the pilot testing phase of the development (see 5.4) as the development of an LDT is an iterative process. The objective is to develop final acceptance criteria which can then be applied to the validation master plan (see 6.2).

5.1.2 Intended use

The medical laboratory shall determine and document the intended use of the planned LDT.

The following information on the planned LDT shall be specified, if applicable:

— indications for use including area of application and intended population;

— methodology;

— biological reference intervals;

— reporting and interpretation of results;

— materials or procedures to allow for metrological traceability;

— preanalytical conditions for specimens;

— further preparatory activities for the examination;

— qualification of staff;

— storage, retirement and disposal of the LDT and its components.

NOTE If the intended use changes at any time, LDT performance specifications can be adapted, and revalidation can be necessary.

5.1.3 Scientific validity

The medical laboratory shall identify and document the scientific validity within the intended population per intended use of the LDT.

NOTE Scientific validity can be derived from research and supported by studies evaluating the analyte for potential clinical applications. Literature review, and where applicable, either feasibility or scientific validity studies, or both, performed by the laboratory will help to establish the potential scientific validity. As the scientific and medical knowledge further develops, the initially established scientific validity can either change or expand, or both.

5.1.4 Scientific literature

The medical laboratory shall compile the scientific literature relevant for the specified purpose and the performance characteristics of the LDT. By doing so, the required level of evidence and the level of equivalence between the LDT and available data from literature shall be taken into account.

When compiling the literature, appropriate consideration should be given to positive and negative indications regarding the performance of the LDT.

Data collected by the medical laboratory in conjunction with the planned LDT shall be assessed in connection with the scientific literature.

The fulfilment of the applicable requirements according to the essential principles for safety and performance as derived from the scientific literature and, if applicable, from data collected by the medical laboratory, shall be evaluated and documented.

NOTE The level of evidence necessary for fulfilling the requirements according to the essential principles depends, among other things, on the results of the risk evaluation.

5.2 Risk management

5.2.1 Risk management system

The medical laboratory shall have a risk management system in place that includes appropriate processes for the analysis, evaluation, control, monitoring, and documentation of risks throughout the lifecycle of the LDT.

As a minimum, the following elements shall be implemented:

— an approach for establishing criteria for risk acceptability;

— identification of risks, which include pre-examination, examination and post-examination risks;

— assessment of the risks;

— risk reduction;

— assessment of the overall residual risk.

Risk mitigation strategies shall be in place to reduce any possible harm for the patient, the operator or any other person that can occur from a testing failure due to either the improper development, manufacturing or improper use of a test.

In the case of modifications within the LDT expected service life, the risks shall be reviewed, and appropriate measures shall be taken in accordance with the risk management process.

In cases, where statistical testing is used to provide evidence in the context of risk assessment, the statistical testing principle shall be in conformity with best practice recommendations and shall be documented.

NOTE 1 ISO 22367 deals with risks to patients, laboratory operators and service providers.

NOTE 2 ISO 14971 covers risk management of medical devices, including software as a medical device and IVD medical devices. It intends to assist manufacturers of medical devices to identify the hazards associated with the medical device, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls.

NOTE 3 ISO/TR 20416 describes a proactive and systematic process that manufacturers can use to collect and analyse appropriate data, to provide information for the feedback processes and use this to meet applicable regulatory requirements to gain experience from the post-production activities.

NOTE 4 The risk management process is a continuous iterative process throughout the entire lifecycle of the LDT, requiring regular systematic updating.

NOTE 5 The extent of risk mitigation measures can depend on the type and extent of the modifications.

NOTE 6 In certain cases, it is not possible, or necessary, to perform inferential statistical studies in order to perform valid risk assessments. The amount of data collected to establish performance specifications can vary dependent on the availability of samples, on the accuracy of the LDT needed to fulfil the clinical needs and on the criticality of risks related to the occurrence of erroneous results

5.2.2 Risk differentiation for the LDT

The medical laboratory shall consider the particular risks presented by the LDT.

The risk differentiation for the LDT shall be based on the following criteria:

— the intended use and indications for use as specified by the laboratory;

— the importance of the information to the diagnosis (e.g. sole determinant or one of several), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which can guide a physician;

— the impact of the result (true or false) to the individual and to public health, respectively;

— the technical, scientific and medical expertise of the intended operators of the LDT and of the recipients of the results obtained by the LDT.

Risk mitigation measures shall be proportional to the level of risk associated with the LDT.

NOTE In some jurisdictions, regulators can require medical laboratories to perform a formal risk classification of LDTs that is based on risk classification rules.

5.3 Essential principles for safety and performance

The medical laboratory shall establish the LDT with consideration of essential principles of safety and performance and best practice recommendations.

The medical laboratory shall establish the LDT in such a way that, if applicable:

— the LDT achieves the analytical and clinical performance intended by the laboratory so that the LDT is suitable for its intended use;

— the characteristics and performance of the LDT are not adversely affected, when the LDT is subjected to stresses which can occur during normal conditions of use;

— the performance characteristics of the LDT are maintained during the expected service life of the LDT;

— the LDT is properly maintained and calibrated in accordance with the laboratory's specifications;

— the characteristics and analytical performance of the LDT components which are adversely affected by transport or storage are documented (e.g. through shock, vibrations, and fluctuations of temperature and humidity);

— the stability of the LDT components is maintained during the shelf-life, during the time of use after being opened, and during transportation;

— if the LDT is intended to be used in combination with other medical devices or IVD medical devices and/or equipment, the whole combination, including the connection system is safe and does not impair the specified performance of the LDT;

— the LDT is accompanied by the documented information needed to distinctively identify the LDT.

5.4 Preliminary and pilot testing

Preliminary and pilot testing should be performed prior to validating the LDT.

Preliminary and pilot testing may include one or more cycles to determine the final acceptance criteria for the performance specifications which would then be applied to the validation master plan.

Preliminary testing should also provide the following:

— necessary operator training and experience to perform the test;

— ability to identify factors that can affect performance;

— any necessary limitations to be considered.

NOTE 1 This activity determines the technical aspects of the LDT by demonstrating that the test system has been shown to meet the design and development requirements.

NOTE 2 Refer to Annex A for an example workflow for an LDT lifecycle.

6 Requirements for the performance evaluation of laboratory-developed tests (LDTs)

6.1 Performance evaluation

The medical laboratory shall conduct a performance evaluation for each LDT.

The medical laboratory shall address the appropriate requirements for performance evaluation based on the following criteria:

— identification of applicable safety and performance requirements of the LDT that require support from relevant scientific validity and analytical and clinical performance data;

— identification of specified target patient groups with clear indications, limitations and contra-indications;

— planning for the implementation of the risk management strategies for the LDT (refer to 5.2);

— environmental, health, and safety requirements;

— process for the resolution of discordant data;

— other considerations as required (e.g. regulatory requirements, turnaround time).

NOTE GHTF/SG5/N8:2012 [25] provides criteria for segregation of IVD medical devices according to their degree of novelty and innovation that can also be used by medical laboratories that establish LDTs.

Performance evaluation of an LDT shall include the following:

— planning of the validation including its documentation within a validation master plan (see 6.2);

— validation of the analytical performance of the LDT (refer to 6.3);

— validation of the clinical performance of the LDT (refer to 6.4);

— identification of excluded performance characteristics (refer to 6.5);

— validation and verification of software, if applicable (refer to 6.6);

— documentation of the validation activities including the final acceptance criteria within a validation report (refer to 6.7);

— post-validation activities of verification (refer to 6.8).

6.2 Validation master plan

The laboratory shall develop a validation master plan (VMP) for the LDT.

The VMP shall describe:

— the intended use and application scope of the LDT (e.g. screening, diagnostic, prognostic, monitoring);

— the defined performance characteristics and acceptance criteria;

— the experiments for validation of the LDT.

When developing a VMP, the following elements shall be considered, if applicable:

— the roles and responsibilities of each operator involved;

— a specification of the methods used for validation and for the LDT;

— instrumentation to be used;

— analytes to be detected;

— measuring intervals;

— biological reference intervals;

— sample matrix and storage stability;

— definition of data types generated by the LDT, e.g. numeric, ordinal or nominal;

— reagent preparation and stability (including expiry date);

— calibrator and control preparation and stability (including expiry date);

— reference or comparator method;

— detection and quantification of expected interfering substances (e.g. presence of inhibitors);

— materials or procedures used to allow for metrological traceability;

— automation and computer requirements;

— description of appropriate statistical tools used for validation data analysis;

— sample throughput;

— where the LDT is software or includes software, an identification and specification of reference databases and other sources of data used as the basis for its decision making.

Where any of the above-mentioned elements are not deemed appropriate in the VMP due to the specific LDT characteristics, a justification shall be provided in the plan.

6.3 Analytical performance

6.3.1 General

The medical laboratory shall collect appropriate data on the analytical performance of the LDT.

LDTs shall be characterized by the following analytical performance characteristics, where applicable:

— analytical specificity;

— analytical sensitivity/cut-off;

— detection limit;

— limit of blank;

— quantitation limit;

— linearity;

— measuring interval;

— robustness of the instrument performance;

— bias;

— precision (measurement repeatability and measurement reproducibility);

— accuracy (resulting from trueness and precision);

— recovery;

— analytical system performance;

— calibrator commutability and stability;

— sample stability;

— cross-reactivity;

— carryover;

— stability;

— requirements and characteristics of pre-analytical processes (e.g. characteristics of sample DNA/RNA extraction).

6.3.2 Measurement uncertainty (MU)

MU shall be determined for the LDT.

The MU may be determined prior to, during, or at the end of, the validation process.

NOTE 1 Additional guidance is available in the following documents:

— ISO/IEC Guide 98-3;

— ISO/TS 20914;

— ISO/TR 27877.

NOTE 2 Detailed guidance on MU of calibrators is provided in ISO 17511. For example, guidance is provided on estimating MU based on a repeatability study and calibrator uncertainty values versus estimating MU based on long term imprecision data, where applicable.

6.4 Clinical performance

The medical laboratory shall collect appropriate data on the clinical performance of the LDT.

Where applicable, LDTs shall be characterized by measures of diagnostic accuracy, including, but not limited to:

— diagnostic specificity;

— diagnostic sensitivity;

— positive predictive value;

— negative predictive value.

Whenever possible, real-world data may be incorporated to acquire adequate data and real-world evidence for LDT performance.

The laboratory may prepare a summary of peer-reviewed literature and data characterising the clinical performance of the LDT.

Clinical performance data may be derived from multiple sources such as clinical performance studies, literature, or experience gained by routine diagnostic testing.

NOTE ISO 20916 defines good study practice for the ethical conduct, planning, design, conduct, recording and reporting of clinical performance studies carried out to assess the clinical performance and safety of IVD medical devices.

6.5 Excluded performance characteristics

For any item specified in 6.3 and 6.4 that is determined to be not applicable in the performance evaluation of an LDT, an explanation shall be documented.

6.6 Software verification and validation

Where software is developed by the laboratory and required for the performance of an LDT, software verification and validation shall be conducted as part of the performance evaluation of an LDT.

Software or software components designed and developed by the medical laboratory, software marketed as research use only or licensed software used for an intended use different from the one claimed by the manufacturer, shall be validated by the laboratory.

Software verification shall be conducted when commercial software is used according to the original manufacturer's instructions for use.

NOTE 1 Software can be considered an LDT if its output is used for diagnosis or treatment.

NOTE 2 If the LDT is software only, the life cycle processes for software development as described in IEC 62304 and the requirements for safety as described IEC 82304-1 can be used.

NOTE 3 When software is involved in the context of an LDT, cybersecurity, electromagnetic compatibility and malware aspects can be covered according to the laboratory management system, as applicable.

NOTE 4 ISO 15189 provides additional details for laboratory information systems management.

NOTE 5 Definitions for software verification and validation in IEC 62304 and IMDRF/SaMD WG/N23:2015[22] can be used.

6.7 Validation documentation and final acceptance criteria

The medical laboratory shall have a report, summarizing all the detailed validation data for each LDT available for review.

Where applicable, the report shall include:

— the intended use of the LDT;

— scientific principle of the test system;