SLOVENSKI STANDARD
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Medicinski laboratoriji - Koncepti in specifikacije za oblikovanje, razvoj, izvajanje in uporabo laboratorijsko razvitih testov (ISO/DIS 5649:2023)

Medical laboratories - Concepts and specifications for the design, development, implementation, and use of laboratory-developed tests (ISO/DIS 5649:2023)

Medizinische Laboratorien - Konzepte und Spezifikationen für den Entwurf, die Entwicklung, die Herstellung und den Einsatz hauseigener In□vitro-Diagnostika (laborentwickelte Tests) (ISO/DIS 5649:2023)

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 (ISO/DIS 5649:2023)

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Foreword

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

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).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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, *Clinical laboratory testing and in vitro diagnostic test systems*.

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 must be carried out to an appropriate standard and all work must be 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 analyzed 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 in-vitro diagnostic devices (IVDs) for the specific intended use or there is a requirement for adding additional specification/ approach(es) to a commercial IVD. 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 may include, but are not limited to LC-MS/MS, TOF/MS, NMR, molecular diagnostic testing (e.g., 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 in-vitro diagnostic devices (IVD). These tests are also considered 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 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.

While accreditation to ISO 15189 is not specifically required for the use of this document, this document can be used to provide additional guidance to laboratories using LDTs.

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 might include look backs, rework or revalidation for improvement of the LDT.

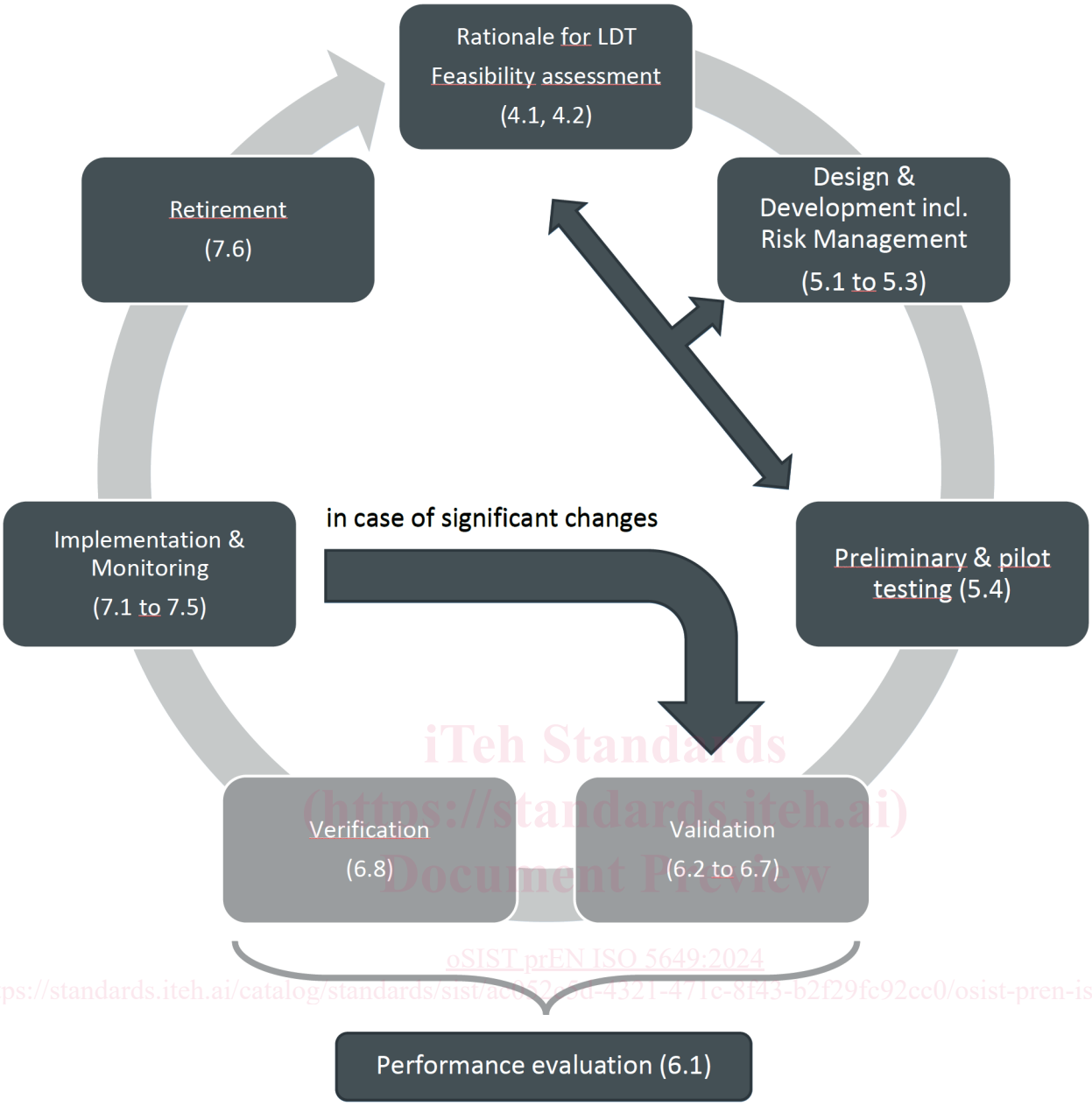

Figure 1 — Possible lifecycle phases of a Laboratory-Developed Test (LDT)

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 could meet requirements for adequate measurement procedure results. Refer to Clauses 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 might 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 Clauses 5.1 to 5.3 of this document.

Preliminary testing precedes performance evaluation phase and determines the technical aspects of the LDT by demonstrating that the LDT meets the design and development requirements. Refer to Clause 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 Clauses 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 Clause 6.8 of this document for verification.

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

LDTs that need replacement shall be retired. Refer to Clause 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 standard 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 the standard 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 cover requirements for examination procedures developed by research or academic laboratories developing and using testing systems for non-in-vitro-diagnostic purposes. However, the concepts presented in this document may also be useful for these laboratories.

The proposed standard does not apply to the design, development and industrial production of commercially used IVD medical devices.

Note International, national, or regional regulations or requirements can also apply to specific topics covered in this document.

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 of a laboratory-developed test
analytical performance of an LDT
ability of an LDT 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 FINAL:2018, 3.2, modified – "IVD Medical Device" has been replaced with "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 sensitivity of a measurement procedure 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* (3.31) can be due to *cross-reactivity* (3.11).

Note 3 to entry: Specificity of a *measurement procedure* (3.31) 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 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]