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



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Australasian Association for Clinical Biochemistry and Laboratory Medicine
Australian Institute of Medical and Clinical Scientists
Australian Society for Microbiology
Human Genetics Society of Australasia
IVD Australia
Medical Technology Association of Australia
National Association of Testing Authorities Australia
National Pathology Accreditation Advisory Council
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Public Pathology Australia
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A Standard always has the following parts:

(i) The Preface states who developed the Standard, what the Standard is aiming to do, and how it relates to other documents.

(ii) The Scope states what the Standard is about, what it covers and what it does not cover.

(iii) The Normative references clause lists other documents that are referenced in the Standard as part of requirements.

(iv) The Terms and definitions clause defines important terms to help with understanding the Standard.

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(1) A normative appendix sets additional requirements that need to be conformed to.

(2) An informative appendix provides additional information or guidance. They usually do not contain requirements. If an informative appendix does contain requirements, the Standard will explain when those requirements apply

(3) A Bibliography lists documents referenced in the Standard but not as part of requirements.

Many Standards include notes. Notes provide recommendations and/or guidance only. They never contain requirements.

Preface

This Standard was prepared by the Standards Australia Committee HE-029, Clinical Laboratory Testing and In Vitro Diagnostic Test Systems.

The objective of this document is to specify 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.

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

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.

This document is identical with, and has been reproduced from, ISO 5649:2024, *Medical laboratories — Concepts and specifications for the design, development, implementation and use of laboratory-developed tests*.

As this document has been reproduced from an international document, a full point substitutes for a comma when referring to a decimal marker.

Australian or Australian/New Zealand Standards that are identical adoptions of international normative references may be used interchangeably. Refer to the online catalogue for information on specific Standards.

The terms “normative” and “informative” are used in Standards to define the application of the appendices or annexes to which they apply. A “normative” appendix or annex is an integral part of a Standard, whereas an “informative” appendix or annex is only for information and guidance.

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Contents

Preface ... **iii**

Foreword ... **v**

Introduction ... **vi**

1 Scope ... **1**

2 Normative references ... **1**

3 Terms and definitions ... **1**

4 General requirements ... **16**
4.1 Rationale for laboratory-developed tests (LDTs) ... 16
4.2 Feasibility assessment ... 17
4.3 Management system ... 17
4.3.1 General ... 17
4.3.2 Transfer of laboratory-developed tests (LDTs) ... 18
4.3.3 Control of subcontractors ... 18

5 Requirements for the design and development of laboratory-developed tests (LDTs) ... **19**
5.1 Determination of LDT performance specifications ... 19
5.1.1 General ... 19
5.1.2 Intended use ... 19
5.1.3 Scientific validity ... 20
5.1.4 Scientific literature ... 20
5.2 Risk management ... 20
5.2.1 Risk management system ... 20
5.2.2 Risk differentiation for the LDT ... 21
5.3 Essential principles for safety and performance ... 21
5.4 Preliminary and pilot testing ... 22

6 Requirements for the performance evaluation of laboratory-developed tests (LDTs) ... **22**
6.1 Performance evaluation ... 22
6.2 Validation master plan ... 23
6.3 Analytical performance ... 24
6.3.1 General ... 24
6.3.2 Measurement uncertainty (MU) ... 24
6.4 Clinical performance ... 25
6.5 Excluded performance characteristics ... 25
6.6 Software verification and validation ... 25
6.7 Validation documentation and final acceptance criteria ... 26
6.8 Post validation activities of verification ... 27

7 Implementation, monitoring and retirement of laboratory-developed tests (LDTs) ... **27**
7.1 Transfer into routine use ... 27
7.2 Result reporting and interpretation ... 28
7.3 Maintenance ... 28
7.4 Monitoring and review activities ... 28
7.5 Change management ... 28
7.6 Retirement of laboratory-developed tests (LDTs) ... 29

Annex A (informative) **Example workflow for a laboratory-developed test (LDT) lifecycle** ... **30**

Bibliography ... **32**

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).

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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.

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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.

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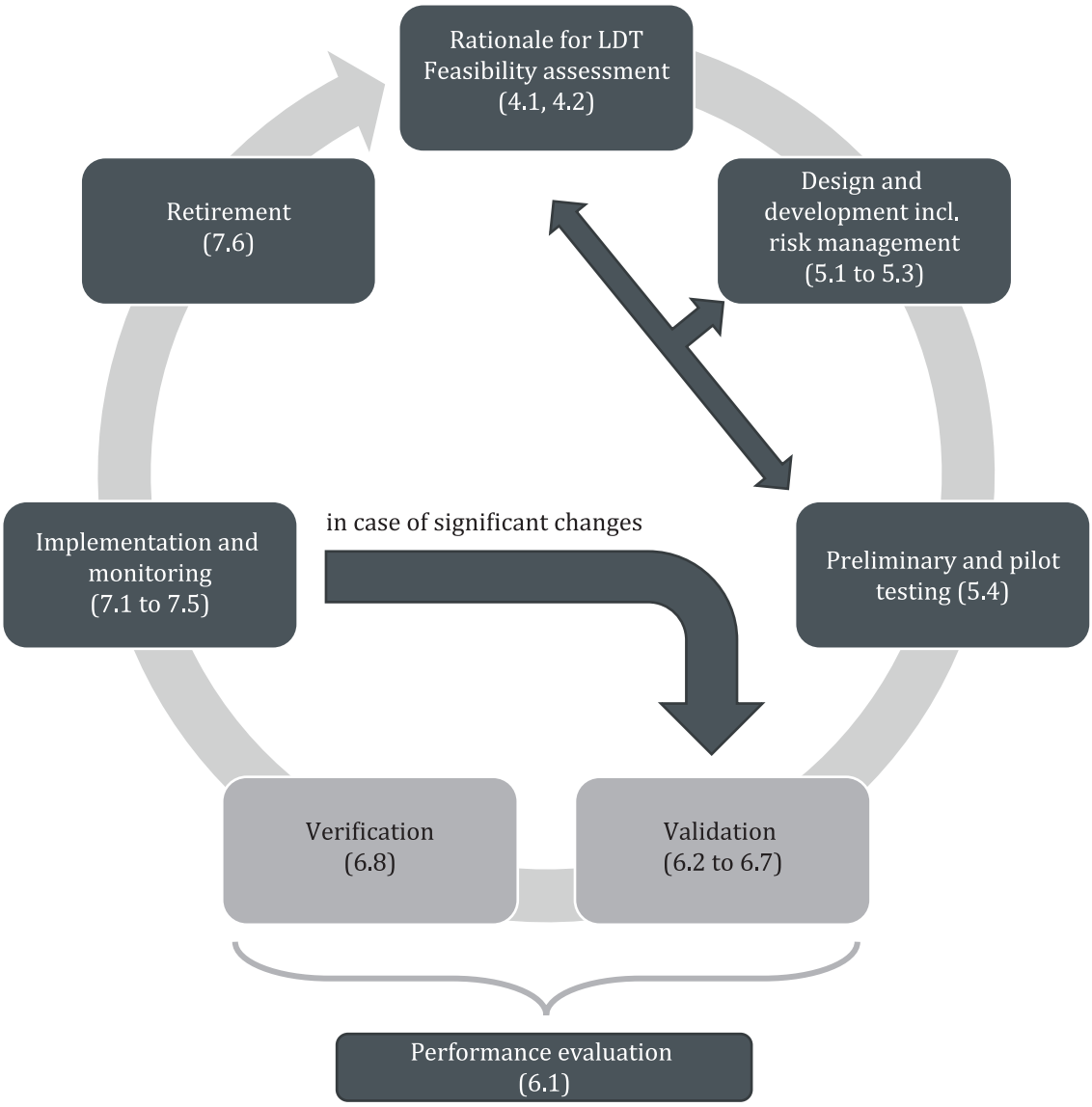


Figure 1 — Possible lifecycle phases of an LDT

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.

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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.

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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”.]

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