CSA Group

Z316.8-18
National Standard of Canada

Requirements for the design, development, and validation of laboratory-developed tests used for the screening, diagnosis, and management of clinical conditions

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Preface

This is the first edition of CSA Z316.8, *Requirements for the design, development, and validation of laboratory-developed tests used for the screening, diagnosis, and management of clinical conditions*.

CSA Group gratefully acknowledges that the development of this Standard was made possible, in part, by the financial and in-kind support from the Canadian Agency for Drugs and Technologies in Health (CADTH), the Canadian Society for Medical Laboratory Science (CSMLS), Alere ULC, Siemens, and Roche.

This Standard was prepared by the Subcommittee on Lab-Developed Tests, under the jurisdiction of the Technical Committee on Medical Laboratory Quality Systems and the Strategic Steering Committee on Health Care Technology, and has been formally approved by the Technical Committee.

This Standard has been developed in compliance with Standards Council of Canada requirements for National Standards of Canada. It has been published as a National Standard of Canada by CSA Group.

Notes:

1) *Use of the singular does not exclude the plural (and vice versa) when the sense allows.*
2) *Although the intended primary application of this Standard is stated in its Scope, it is important to note that it remains the responsibility of the users of the Standard to judge its suitability for their particular purpose.*
3) *This Standard was developed by consensus, which is defined by* CSA Policy governing standardization — Code of good practice for standardization *as "substantial agreement. Consensus implies much more than a simple majority, but not necessarily unanimity". It is consistent with this definition that a member may be included in the Technical Committee list and yet not be in full agreement with all clauses of this Standard.*
4) *To submit a request for interpretation of this Standard, please send the following information to inquiries@csagroup.org and include "Request for interpretation" in the subject line:*
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   b) *provide an explanation of circumstances surrounding the actual field condition; and*
   c) *where possible, phrase the request in such a way that a specific "yes" or "no" answer will address the issue.*

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   a) *Standard designation (number);*
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   c) *wording of the proposed change; and*
   d) *rationale for the change.*

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0 Introduction

Medical laboratory professionals have a responsibility to provide services to patients of the highest quality and integrity and to practice their profession with honesty, integrity, and reliability. 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 could lead to patient harm.

[Source: *Ethical practice in laboratory medicine and forensic pathology.* Mohamed M. El-Nageh, et al. WHO Regional Publications, Eastern Mediterranean Series, 1999.]

In most clinical laboratories today, the majority of routine clinical samples are processed and analyzed using commercially available tests on automated instrumentation purchased from various manufacturers of IVD products. In Canada, the sale, advertising for sale, and importation for sale of medical devices is regulated by Health Canada and must undergo stringent assessment by Health Canada before they can be made available for purchase.

However, there are some tests for which there are no commercially available methods or for which modern technology provides a much superior test result. Such tests are referred to as “in-house” or laboratory-developed tests. LDTs can be defined as tests developed (or modified) and used within a single laboratory 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.

As technology continues to advance, more highly complex techniques are being introduced to the medical laboratory. These include LC/MS/MS, TOF/MS, NMR, NGS, molecular diagnostic testing (e.g., PCR), ISH, IHC, and whole slide scanning and imaging. Frequently, these techniques are developed in a clinical research laboratory, transferred to the medical laboratory, and placed into routine use as diagnostic tests. These tests are considered laboratory-developed tests. 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 no standard by which to assess their performance, quality, and reliability.

The purpose of this Standard is to provide requirements on the development and validation of LDTs that have not been subjected to an in-depth validation process and that would be typically expected from those that are commercially developed for licensing or approval by the jurisdiction having authority.

1 Scope

1.1 General

This Standard specifies the minimum requirements and best practices for the development, validation, and use of laboratory-developed tests in clinical and research laboratories for the screening, diagnosis, and management of clinical conditions.

It does not provide specific details on how to achieve these requirements since they are provided in many other sources which are considered current best practice. References to these resources will be provided in this Standard.

Note: *See also Annex A for recommended resources.*

1.2 Inclusions

The Standard is intended to be used by organizations and individuals that are developing LDTs for the purpose of providing results that can be used in the screening, diagnosis, or management of clinical conditions.

1.3 Exclusions

This Standard does not apply to the following:

a) tests developed in-house but distributed outside of the laboratory;

   Note: *Tests distributed outside of the laboratory fall outside the definition of "laboratory-developed test". These are considered to be commercially distributed IVDDs and are regulated by Health Canada under the Medical Devices Regulations.*

b) LDTs that are developed by a laboratory or manufacturer solely for RUO or IUO (i.e., where there is no reporting of patient results); and

c) accredited, non-clinical laboratories which have their own standard for development, validation, and use of LDTs.

The Standard does not apply to laboratory-developed tests that are developed by a laboratory for RUO/IUO until such time that the test becomes applied to clinical testing and has undergone suitable validation according to the requirements in this Standard.

Notes:

1) *The RUO/IUO labeling is meant to serve as a warning to prevent such products from being used in clinical diagnosis or patient management. However, clinical laboratories can validate tests using RUO reagents or components through their own procedures as described in this Standard, and subsequently offer it for clinical diagnostic use as a laboratory-developed test once validated.*
2) *Refer also to the* Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only. Guidance for Industry and Food and Drug Administration Staff *document issued on November 25, 2013, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety.*

1.4 Terminology

In this Standard, "shall" is used to express a requirement, i.e., a provision that the user is obliged to satisfy in order to comply with the standard; "should" is used to express a recommendation or that which is advised but not required; and "may" is used to express an option or that which is permissible within the limits of the Standard.

Notes accompanying clauses do not include requirements or alternative requirements; the purpose of a note accompanying a clause is to separate from the text explanatory or informative material.

Notes to tables and figures are considered part of the table or figure and may be written as requirements.

Annexes are designated normative (mandatory) or informative (non-mandatory) to define their application.

2 Reference publications

This Standard refers to the following publications, and where such reference is made, it shall be to the edition listed below:

Health Canada

Food and Drugs Act , R.S.C., 1985, c. F-27

Medical Device Regulations, SOR/98-282

ISO (International Organization for Standardization)

3534-1:2006
Statistics — Vocabulary and symbols — Part 1: General statistical terms and terms used in probability

5725-1:1994
Accuracy (trueness and precision) of measurement methods and results — Part 1: General principles and definitions

14971-1:1998
Medical devices — Risk management — Part 1: Application of risk analysis

15189:2012
Medical laboratories — Requirements for quality and competence

17025:2005
General requirements for the competence of testing and calibration laboratories

17511:2003
In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials

18113-1:2009
In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 1: Terms, definitions and general requirements

ISO/IEC Guide 98-3:2008
Uncertainty of measurement — Part 3: Guide to the expression of uncertainty in measurement

ISO/NP TS 20914 (under development)
Medical laboratories — Practical guide for the estimation of measurement uncertainty