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SCC Requirements and Guidance for Method Verification and Validation in Testing Laboratories (RG-MVVT)

2021-05-24

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Aussi offert en français sous le titre *Exigences et lignes directrices du CCN – Validation des méthodes dans les laboratoires d'essais*

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Introduction

The Standards Council of Canada (SCC) recognises the significance of method validation as a key requirement to deliver meaningful and reliable results. Method validation is a process that requires several steps in selecting appropriate methods and procedures for all laboratory activities, followed by verification or validation depending on the category of the method.

This document sets out the requirements for, and gives guidance to, applicant and accredited laboratories about the interpretation of the validation requirements for all types of test methods as described in clause 7.2 “Selection, verification and validation of methods” of ISO/IEC 17025:2017.

1. Scope

These general guidelines shall apply to all types of laboratory activities including sampling, regardless of field for the interpretation of the validation and verification requirements for testing methods and additional requirements applicable to most common types of testing. Additional program or sector-specific requirements for validation as outlined in specific Program Specialty Area (PSA) documents will also apply.

2. Normative References

- ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories.
- ISO/IEC Guide 99:2007 International Vocabulary of metrology- Basic and general concepts and associate terms (VIM)
- International vocabulary of metrology – Basic and general concepts and associated terms (VIM), JCGM 200:2012, GUM 2008 with minor corrections
- SCC Requirements and Guidance for the Accreditation of Testing Laboratories.
- SCC Requirements and Guidance for Accreditation of Laboratories Engaged in Test Method Development and Non-Routine Testing
- SCC Requirements and Guidance for the Accreditation for Forensic Testing Laboratories.
- SCC Guidelines for the Presentation of Laboratory Scopes of Accreditation.
- Eurachem/CITAC Guide, The Fitness for Purpose of Analytical Methods. A Laboratory Guide to Method Validation and Related Topics. 2nd edition, 2014.
- Eurachem/CITAC Guide, Quality Assurance for Research and Development and Non-routine Analysis, 1st edition, 1998.
- Eurachem/CITAC Guide CG4, Quantifying uncertainty in analytical measurement, 3rd edition, 2012.

- Evaluation of measurement data – guide to the expression of uncertainty in measurement, Joint Committee for Guides in Metrology, JCGM 100:2008, GUM 1995 with minor corrections.
- IUPAC - Harmonized Guidelines for Single Laboratory Validations of Methods of analysis. Pure Appl. Chem. 74(5), 2002, p 835-855.
- Health Canada Compendium Methods for Chemical and Microbiological Analysis of Foods, https://www.canada.ca/en/health-canada/services/food-nutrition/research-programs-analytical-methods.html
- Official Journal of the European Communities (2002) Commission Decision of 12 August 2002 Implementing Council Directive 96/23/EC Concerning the Performance of Analytical Methods and the Interpretation of Results. Official Journal of the European Union, C (2002), 3044

3. Informative References

- Supplement to Eurachem Guide on the Fitness for Purpose of Analytical Methods, Planning and Reporting Method Validation Studies, Planning and Reporting Method Validation Studies –, 1st edition,2019).
- Eurachem/CITAC Guide, Setting and Using Target Uncertainty in Chemical Measurement, 1st edition,2015).
- ILAC G19:08/2014 Modules in a Forensic Science Process.
- AOAC INTERNATIONAL Methods Committee Guidelines for Validation of Qualitative and Quantitative Food Official Methods of Analysis. J AOAC Int'l 85(5) 2002, p.1187-1200.
- Protocol for the Design, Conduct and Interpretation of Collaborative Studies. Pure Appl. Chem, 60(6), 1988, p 855-864.

4. Definitions

Method: similar to "measurement procedure" defined in Guide 99.
Measurement procedure: a set of operations, described specifically, used in the performance of particular measurements according to a given method. It is usually recorded in a document that sometimes itself called a "measurement procedure" (or a **measurement method**) and is usually insufficient detail to enable an operator to carry out a measurement without additional information. (Guide 99)
Measurement procedure (JCGM 200, item 2.6): 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: A measurement procedure is usually documented in sufficient detail to enable an operator to perform a measurement.
NOTE 2: A measurement procedure can include a statement concerning a target measurement uncertainty.

NOTE 3 A measurement procedure is sometimes called a standard operating procedure, abbreviated SOP.

Verification (referred to as Method Verification): The process of ensuring that the laboratory has the ability to perform a previously validated method consistent with the requirements of the method and the needs of the laboratory.

Validation (referred to as Method Validation): The process of ensuring that a method has the capabilities and performance characteristics consistent with specified requirements and that it's fit for the intended use and designed application.

Fitness for Purpose: (IUPAC Harmonized Guidelines for Single Laboratory Validations of Methods of analysis.): It is the extent to which the performance of a method matches the criteria, agreed between the analyst and the end-user of the data, that describe the end-user's needs. Fitness-for-purpose criteria will ultimately be expressed in terms of acceptable combined uncertainty.

Standard Published Method: international, regional or national standards or other recognized reputable technical organizations available in the latest valid version or in relevant scientific texts or journals, or as specified by the manufacturer of the equipment unless it is not appropriate or possible to do so (ISO/IEC 17025, clause 7.2.1.4)

Modified method: standard and non-standard methods used outside their intended scope or otherwise modified.

In-house method: A method in-house developed by the laboratory for its own use.
(e.g. laboratory-developed method)

Performance criteria: requirements for a performance characteristic according to which it can be judged that the analytical method is fit for the purpose and generates reliable results (EC Directive, 2002).

5. Selection of Test Methods

Often, the customer specifies the method to be used, which may or may not be a standard published method. Standard published methods are preferred, but the laboratory may use ones published by technical organizations, supplied by equipment manufacturers, published in scientific literature, or developed by the laboratory, provided the customer is in agreement and these non-standard methods have been validated before use. The degree of validation required will be discussed in Section 7.

Validation does not apply to standard published methods in terms of the requirement of ISO/IEC 17025 clause 7.2.2. Verification does apply to standard published methods as described in clause 7.2.1. of ISO/IEC 17025.

It is recognized that for laboratories to be responsive to customer's needs and changing technology, new methods will need to be implemented or existing methods modified on a regular basis. Refer to the following documents designed to address some of these issues within the following Program Specialty Areas:

- *SCC Requirements and Guidance for Accreditation of Laboratories Engaged in Test Method Development and Non-Routine Testing*.
- *SCC Requirements and Guidance for the Accreditation for Forensic Testing Laboratories*

6. Verification of Test Methods

Modified methods may consist of deviation(s) from a standard reference method or a prescriptive procedure for use on an on-going basis. If the laboratory can demonstrate the deviation(s) is (are) not significant, then a verification according to clause 7.2.1 of ISO/IEC 17025 standard will be required.

The laboratory shall verify that it can properly perform methods before introducing them by ensuring that it can achieve the documented performance characteristics according to clause 7.2.1.5 of ISO/IEC 17025.

When standard published methods are adopted by the laboratory without significant deviations, verification is required under following examples but may not be limited to:

- Confirmation that the implementation of the standard published method is fit for the intended purpose (e.g. precision, bias, linearity, interference, robustness, grounding, linearity, electrical connections, physical stability are consistent with the ones published in the reference method);
- Estimation of key performance parameters such as method detection limit (MDL), reporting limit (RL) or signal-to-noise ratio for representative matrices, or types of samples under test (Annex A for examples of performance parameters).
- Evaluation of measurement uncertainty;

- Confirmation that the method works reliably and accurately with the typical samples processed (e.g. acceptable spiked sample recovery, or comparison against an independent reference or other validated test method);
- Confirmation that any decision rule associated with the method is valid for the laboratory's implementation.

If guidelines within a particular PSA specify verification requirements, these shall also be followed.

7. Validation Process

7.1. Extent of Validation

Validation shall apply for the following categories of method according to clause 7.2.2.1 of ISO/IEC 17025:

- non-standard methods (in-house);
- laboratory-designed/developed methods (in-house);
- standard methods used outside their intended scope (modified);
- significant modifications of standard methods that could impact the reliability of results (modified).

The stated purpose of the validation is to confirm that the methods are fit for the intended use. In addition, clause 7.2.2. states that:
"*The validation shall be as extensive as is necessary to meet the needs of the given application or field of application".*

The table below is meant to summarize requirements based on verification or validation of categories of test methods commonly performed in testing laboratories.

Test method category	Validation or verification requirements
Standard Published Method	Verification of published performance characteristics against the laboratory's method performance in accordance with the requirement of ISO/IEC 17025 clause 7.2.1.5.
Standard Published Method that has been modified by the laboratory or another entity (e.g. different matrices, concentration ranges, analytes, standard published method used or a similar purpose but different conditions)	Validation is required and the extent will vary based on the risk associated with the conducted analysis.
In-house developed method	Validation

Method published in the scientific literature with/without any performance data	Validation
Changes in implementation of a previously validated method (e.g. changes to equipment, reagents, lab environment or staff)	Verification will suffice. The extent will vary in order to demonstrate changes do not have a significant impact on performance characteristics.
Archived standard published or previously validated method that is reinstated	Verification of previous performance characteristics
Ad hoc or special analyses	Extent of validation limited by circumstance
Commercial Test Kits - collaboratively tested, third party evaluation (e.g. AOAC)	Verification of published performance characteristics but validation may be required if any changes are made.
Commercial Test Kits - no performance data available, incomplete or not applicable for the matrix being tested	Validation
Instrument manufacturer's method which is not published in a scientific journal	Verification if instrument manufacturer's method criteria is available and complete. Validation if instrument manufacturer's method criteria is not present or incomplete.

7.2. Performance Characteristics and Criteria of a Test Method

Refer to Annex A of this document for a list of applicable parameters (characteristics). Validation should also evaluate sampling, sub-sampling and transportation of samples to the laboratory, where these can affect the method outcome or where there are sample acceptance criteria and where the laboratory is responsible for these activities. Also, to be considered are interpretations of population results, incorporating statistics as applicable. Where the laboratory is responsible for sampling or sub-sampling, the method validation shall ensure that there are no negative impacts on population results. Statistics may be used as applicable. The terminology used to describe the performance characteristic may vary among disciplines and should be defined by the laboratory as necessary for clarity (see Annex A for examples).

In addition to relevant parameters (characteristics), a validation summary should include the following:

- Reference (e.g. identify technical records for more details)
- Measurand
- Type of sample(s), (e.g. description of the tested matrices)
- Type of measurement (e.g. qualitative, semi-quantitative, quantitative, determinative)
- Method status (routine or non-routine)

- Description of the intended use (e.g., legal, regulation, as agreed with customer [screening, confirmatory, exploratory, process control, others])

In some disciplines, the guidelines available to the laboratory testing community are extensive. It is therefore the responsibility of the laboratory, with input from customers, to seek out the relevant characteristics to be evaluated with respect to the laboratory's specific situation and the customer's needs. The laboratory must have a documented validation plan, either to be used generally or applied to a specific project or customer. Test method performance characteristics to be evaluated will vary with the type of test and its intended use. Discipline-specific or customer required performance criteria are to be applied to demonstrate fitness for purpose.

7.3. Approaches used in Validations

Validations must address the reliability (or repeatability) and reproducibility of the test method and also the ability to produce correct results which are related to the accuracy or trueness of results. To demonstrate accuracy, there must be a comparison against an independent known reference resulting in consistent outcomes and maintaining metrological traceability.
Materials used to evaluate test method performance must be representative of those to be analyzed when the test method is in routine use. Certified reference materials should be used to assess trueness, when available. Previously analysed proficiency testing samples, such as those available from proficiency testing exercises can be used to assess bias. However, reference materials can underestimate the variation seen in test samples. The use of naturally contaminated or naturally occurring samples if available should be considered. The method under validation can be compared to an established standard method and the bias between the two methods determined. Often reference materials or a standard method are not available. Recovery studies are conducted by spiking field blanks with a known amount of analyte or organism. Blanks must be representative of typical samples received for testing, so validations may need to be conducted on several different blanks obtained from several sources. In many biological systems, experiments are conducted to generate naturally occurring materials.

7.4. Uncertainty Evaluation

A robust estimation of measurement uncertainty must be performed as part of the validation. Some standard methods have already published uncertainties which should be used as a starting point in determining the laboratory's own evaluation. Please refer to *SCC Requirements and Guidance for the Accreditation of Testing Laboratories*, clause 7.6 for further details.

For detailed discussions of uncertainty evaluations in validation studies see the following:
- Eurachem / CITAC Guide, Quantifying Uncertainty in Analytical Measurement
- IUPAC's Harmonized Guidelines for Single-Laboratory Validation of Methods of Analysis (Appendices A14 and B)
- Evaluation of measurement data – guide to the expression of uncertainty in measurement, JCGM 100:2008, GUM 1995 with minor corrections.

It is important to recognize that some significant sources of uncertainty may not be covered in multi-laboratory or single laboratory validations. Ruggedness testing conducted during the validation study can provide information of the effect of some parameters. The Eurachem Guide recommends that precision should be estimated over time and to include the natural variation of all factors. This includes data generated by quality control samples, replicates, proficiency testing material, etc.

For quantitative and semi-quantitative method, an estimate of uncertainty is required, while for qualitative methods an identification of sources of uncertainty and under which conditions they are controlled is necessary.

8. Documentation

The laboratory must have available for review indexed records, summarizing the detailed method validation / verification data for all non-standard, in-house developed or modifications and amplifications of standard published methods. These records shall include:

- The test method including information about equipment, reagents, calibration etc.
- Reference to the validation procedure or plan used to generate method performance characteristics.
- Test method performance characteristics and how these were calculated or defined. The raw data should be available for review.
- Test method performance criteria against which the characteristics were evaluated and whether or not the method is fit for purpose.
- Review and authorization of the report by a competent authorized person.
- The intended use of the method including relevant matrices.
- Estimates of uncertainty.

If a method that is not a standard published method is used routinely, often over time there will be modifications or improvements made. This information needs to be documented and available for assessment. Ongoing proficiency testing data and quality control data should be reviewed by the laboratory to confirm the fitness of the method. The validation/verification information shall be kept according to the timeline established by the laboratory under the requirements of clause 8.4.2 of ISO 17025.

Annex A: Performance Characteristics (parameters) to be considered by the laboratory when conducting method development and validation:

The list below serves as a guide for characteristics or parameters that a laboratory should consider when developing and validating a test method. Performance characteristics (parameters) and the acceptance criteria used to evaluate the performance characteristics shall take into account:

- the intended use of the test method including customer needs: “the extent of validation, and the consequences in time and cost, are one of the key issues to be agreed upon between analyst and customer when commissioning method development.” (Eurachem/ CITAC Guide - Quality Assurance for Research and Development and Non-routine Analysis, section 6.8.5.4)
- the discipline: some characteristics, including the definitions, are discipline or test type specific.
- the type of test (qualitative, quantitative) and purpose (screening, confirmatory).

Characteristics or criteria to be considered may include, but are not limited to:

- Accuracy
- Action levels (for regulatory analyses)
- Analytical specificity* (selectivity, exclusivity, inclusivity)
- Calibration (see linearity, range)
- Confirmation
- Diagnostic selectivity*, Diagnostic sensitivity*
- Efficacy
- False positive rate, False negative rate (paired studies)
- Ion Suppression for LC/MS or LC/MSMS assay
- Limit of detection (detection capability, decision limit, level of detection)
- Limit of determination (limit of quantitation)
- Linearity (calibration, range)
- Measurement bias
- Measurement uncertainty
- Precision
- Predictive value
- Probability of detection (unpaired studies)
- Range (see calibration, linearity)
- Recovery
- Relative Sensitivity, Relative Specificity
- Repeatability
- Reporting limit
- Reproducibility
- Ruggedness/robustness
- Selectivity*, Sensitivity*, Specificity*

- Stability (of analyte, organism, sub-samples, extracts)
- Target organisms
- Test controls (including reference populations)
- Thresholds

** Definitions for some terms may vary among disciplines. For example, the term, "selectivity," is recommended for analytical chemistry instead of "specificity" (see IUPAC definition). Some definitions such as analytical specificity, diagnostic selectivity and diagnostic sensitivity are used in biological testing.*

Annex B: Guideline for validation of test methods in Agriculture Inputs, Food, Animal Plant-Protection (AFAP) - PSA

In some sectors, validation typically refers to interlaboratory studies such as those conducted by a sector-specific technical organization. A test method is evaluated with different analysts in a number of different laboratories usually using different equipment and materials. For example, AOAC International organizes collaborative studies in food analysis. Interlaboratory validation may be a requirement in some fields of regulatory analyses. The International Union of Pure and Applied Chemistry (IUPAC) published Protocol for the design, conduct and interpretation of collaborative studies, which was accepted by 27 participating organizations as the minimum requirement for these studies. However, due to time constraints, availability of resources and the need to address emerging issues, new hazards or new products methods cannot always be subjected to full interlaboratory validations. In some specialized testing areas, it is difficult to find a sufficient number of participants.

IUPAC's Harmonized Guidelines for Single-Laboratory Validation of Methods of analysis provides some general guidelines for the extent of single laboratory validation studies.
For laboratories under the AFAP – PSA that are performing food microbiology under legislation enforced by Canadian Food Inspection Agency (CFIA), the Health Canada Compendium of Analytical Methods are validated and considered standard reference methods. These methods are current and updated through a joint Health Canada -CFIA committee, therefore the methods are actively used for regulatory testing. The Compendium of Methods of Analytical Methods are ready reference methods used by Health Products and Food Branch (HPFB) of Health Canada in the areas of food chemical analysis. Official Methods used for chemical analysis of foods are HPB methods which are laboratory procedures for surveillance used in support of Health Canada's regulatory compliance inspection programs and considered validated if used as published All the described methods are validated only for a very specific set of matrices. Therefore, proper validation must be completed prior to using these methods for matrices outside the original scope of the method.

The AOAC food matrix triangle is a common tool used to assist laboratories in selecting matrices to be included in their studies. The AOAC food triangle is constructed based on the relative levels of fat, protein and carbohydrate divided into nine sectors. Consequently, validation is required to be performed over a wide variety of foods since subsequent steps of preparation, extraction and testing may be different for a sample containing 100% carbohydrate compared to a sample that is high in lipids. While planning method validation studies, samples that are reflective of the types of samples received by the laboratory should be considered including samples that might be a challenge to analyze (e.g. high fat, high protein, high moisture). Analysts' professional judgement will be required when validating a certain segment of the food triangle; other factors should be considered such as extraction technique, solids vs. liquid ratio and matrix interferences.