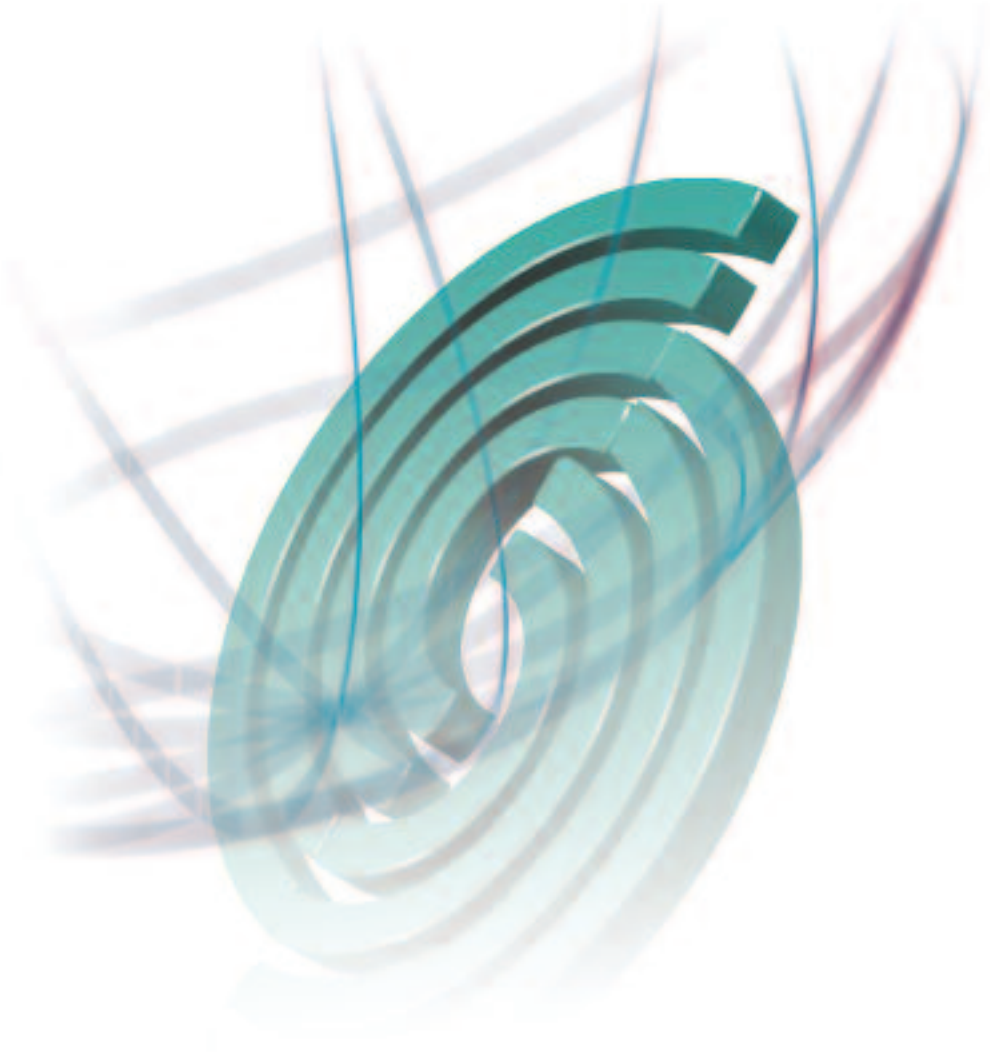

Standards Council of Canada
Conseil canadien des normes

PALCAN Guidance for the Validation of Test Methods

CAN-P-1629
November 2006

Canada

PALCAN
GUIDANCE FOR
THE VALIDATION OF TEST METHODS

POLITIQUE DU PALCAN
CONCERNANT LA VALIDATION
DES MÉTHODES D'ESSAIS

CAN-P-1629
November 2006

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FOREWORD

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The mandate of the Council is to promote the participation of Canadians in voluntary standards activities, promote public-private sector cooperation in relation to voluntary standardization in Canada, coordinate and oversee the efforts of the persons and organizations involved in the National Standards System, foster quality, performance and technological innovation in Canadian goods and services through standards-related activities, and develop standards-related strategies and long-term objectives.

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This document is one of several issued by the Standards Council of Canada to define the policies, plans, and procedures established by the Council to help achieve its mandate.

Requests for clarification and recommendations for amendment of this document, or requests for additional copies should be addressed to the publisher directly at info.palcan@scc.ca .

1 PURPOSE

To provide applicant laboratories, accredited laboratories and PALCAN Team Leaders and Assessors with guidance about the interpretation of the validation requirements for non-standard and in-house developed test methods as described in 5.4.5.2 of CAN-P-4E.

2 SCOPE

These general guidelines should apply to all types of laboratories, regardless of field, but additional program or sector-specific requirements as outlined in specific Program Specialty Area (PSA) documents will also apply. See the reference list for some examples and relevant PSA criteria and checklists.

Interpretations of ISO/IEC 17025:2005 section 5.4.5 can be found in this document, as well as CAN-P-1630 and the CAN-P-PSA documents. In case of disagreement, the CAN-P-PSA document shall prevail.

3 DEFINITIONS

3.1 Validation: (ISO 9000:2000): Confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use are fulfilled.

3.2 Verification: (ISO 9000:2000): Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

3.3 Method Validation: (Eurachem): The process of establishing the performance characteristics and limitations of a method and the identification of the influences which may change these characteristics and to what extent. Which analytes can it determine in which matrices in the presence of which interferences? Within these conditions what levels of precision and accuracy can be achieved? The process of verifying that a method is fit for purpose; i.e. for use for solving a particular analytical problem.

3.4 Fitness for Purpose: (IUPAC): Degree to which data produced by a measurement process enables a user to make technically and administratively correct decisions for a stated purpose.

The Eurachem Guide, *The Fitness for Purpose of Analytical Methods. A Laboratory Guide to Method Validation and Related Topics*. Edition 1.0 - 1998, Annex A contains a complete set of definitions related to validation.

3.5 Standard Published Method: Refer to CAN-P-1570 PALCAN Handbook Appendix B section 4.

4 SELECTION OF TEST METHODS

Often, the client 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, or published in the scientific literature or developed by the laboratory, provided the client is in agreement and these non-standard methods have been validated before use. The degree of validation required will be discussed in Section 5.

Validation does not apply to standard published methods in terms of the requirement of ISO/IEC 17025:2005 section 5.4.5.

Refer to CAN-P-1570 PALCAN Handbook Appendix B section 4 which discusses the different categories of methods allowed on a scope of accreditation.

It is recognized that for laboratories to be responsive to client's needs and changing technology, new methods will need to be implemented or methods modified on a regular basis. The Program Specialty Area of Test Method Development & Evaluation and Non-Routine Testing is designed to addresses some of these issues. Refer to CAN-P-1595 available on the SCC website at: http://www.scc.ca/en/programs/lab/publications.shtml .

5 VALIDATION PROCESS

5.1 Interlaboratory vs. single laboratory validation

In some sectors, full validation typically refers to interlaboratory study such as 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 a document in 1988, *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 can not always be subjected to full interlaboratory validations. In some specialized testing areas it is difficult to find a sufficient number of participants.

Recognizing that there is a need for single laboratory validations and that this is the norm in many fields, a Food and Agriculture Organization (FAO)/International Atomic Energy Agency (IAEA) expert consultation (Section 8 - References, item 8.7) recommended that validations in a laboratory be conducted according to five general principles. Although these principles are recommended for food control analyses, they may be applied more generally:

- The laboratories operate under an internationally recognized quality system.
- The laboratories have a third party review of their validation process.
- Analytical methods are assessed in respect to the general criteria for selection of methods (in the case of food control criteria according to Codex).
- The validation is documented in a report which clearly states the scope of the method.
- Evidence of transferability is provided.

IUPAC's *Harmonized Guidelines for Single-Laboratory Validation of Methods of analysis* provides some general guidelines for the extent of single laboratory validation studies.

5.2 Extent of Validation

CAN-P-4E, clause 5.4.5.2, states that laboratory shall validate:

- non-standard methods;
- laboratory-designed/developed methods;
- standard methods used outside their intended scope;
- amplifications and modifications of standard methods.

The stated purpose of the validation is to confirm that the methods are fit for the intended use. In addition the clause 5.4.5.2 states that:

- The validation shall be as extensive as is necessary to meet the needs of the given application for field of application.
- The laboratory shall record the results obtained, the procedure used for the validation, and a statement as to whether the method is fit for the intended use."

"Validation is always a balance between costs, risks and technical possibilities". (CAN-P-4E: clause 5.4.5.3- Note 3)

If performance standards have been published and are used as standard published methods, it is expected that the laboratory demonstrates or confirms that it can achieve those standards. Some documents refer to this exercise as a "verification" or partial validation exercise. The requirement in CAN-P-4E that applies to confirmation in regard to a standard published methods and the ability of a laboratory to produce a competent result is under the requirement of CAN-P-4E section 5.4.2 and is not truly validation in the manner intended by CAN-P-4E section 5.4.5

Test method description	Validation or verification requirements
Standard Published Method	Confirmation of published performance characteristics in accordance with the requirement of ISO/IEC 17025:2005 section 5.4.2. Validation may be required only if any changes made, in accordance with the requirements of ISO/IEC 17025:2005 section 5.4.4 for non-standard methods.
In-house developed method	full validation
Method published in the scientific literature without any performance data	full validation
Methods published in scientific literature with performance data	Confirmation of published performance characteristics, but more likely full validation required according to ISO/IEC 17025:2005 section 5.4.5.
Changes in implementation of previously validated method - i.e. changes to equipment, reagents, lab environment or staff.	Extent of validation will vary to demonstrate change does not have a significant impact on performance characteristics
Standard published method applied to different matrices, different concentration ranges, analytes or standard published method used for a similar purpose but different conditions.	Validation is required and the extent will vary. e.g. having similar properties to those of representative matrices and analytes
Archived standard published or previously validated method that is reinstated	Confirmation 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)	Confirmation 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	validation

5.3 Performance Characteristics and Criteria of a Test Method

Performance characteristic "means functional quality that can be attributed to an analytical method" (EC Directive). Examples of typical performance characteristics include: selectivity, accuracy, trueness, recovery, precision, repeatability, reproducibility, detection limit, limit of quantitation, detection capability, ruggedness and stability. The validation may also evaluate sampling, sub-sampling and transportation of samples to the laboratory.

Performance criteria "means 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).

How test method performance characteristics are evaluated, along with the criteria against which they will be assessed, are usually described in detail in discipline-specific documents. Program Specialty Area criteria may list some performance characteristics to be found in validation documentation. SCC documents such as CAN-P-1579, *Guidelines for the Accreditation of Mineral Analysis Testing Laboratories* provide detailed guidance on validation. In some disciplines the guidelines available to the laboratory testing community are extensive. It is therefore the responsibility of the laboratory, with input from clients, to seek out the relevant characteristics to be evaluated with respect to the laboratory's specific situation and client's needs. The laboratory must have a documented validation plan, either to be used generally or applied to a specific project or client. Test method performance characteristics to be evaluated will vary with the type of test and its intended use. Discipline-specific or client required performance criteria are to be applied to demonstrate fitness for purpose.

There are widely accepted criteria for repeatability, reproducibility and trueness (or recovery) for the analysis of pesticide and veterinary drug residues based on analyte concentration. The Horwitz equation can be used to predict the reproducibility standard deviation.

5.4 Approaches used in Validations

Materials used to evaluate test method performance must be representative of those to be analyzed when the test method is in routine use. Methods should be validated using certified reference materials which can be used to assess trueness, when available. Reference materials such as those available from proficiency testing exercises can be used to assess bias. However, reference materials may underestimate the variation seen in test samples. The method under validation may 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 need to be conducted on several different blanks obtained from several sources. In many biological systems experiments are conducted to generate naturally occurring materials.

5.5 Uncertainty Estimates and Validation

For detailed discussions of uncertainty estimates in validation studies see Section 7.6 and 7.7 of the Eurachem/CITAC Guide, *Quantifying Uncertainty in Analytical Measurement* and appendices A and B of IUPAC's *Harmonized Guidelines for Single-Laboratory Validation of Methods of Analysis.* 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.

6 DOCUMENTATION

The laboratory must have available for review a report, summarizing all the detailed method validation data for all non-standard, in-house developed or modifications and amplifications of standard published methods. . The report should include:

- The test method as validated. This includes information about equipment, reagents, calibration etc. (Confusion may arise if the method does not meet performance criteria and further method development is required).
- Reference to the validation procedure or plan used to generate the test method performance characteristics.
- A summary of the test method performance characteristics and how these were calculated or defined. The raw data should also be available for review.
- The test method performance criteria against which the characteristics were evaluated and whether or not the method is fit for purpose.
- The intended use of the method.
- Estimates of uncertainty.

If the method that is not a standard published method is used routinely, it is expected that over time there will 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 information should be kept as long as the method is in routine use.

The format for the validation report is outlined in either of the following documents:

- Client specified requirements and/or
- Laboratory validation plan or procedure and/or
- CAN-P-PSA criteria, where applicable.

7 GUIDELINES FOR ASSESSORS

What should assessors be looking for?

- How are test methods selected by the laboratory?
- Is the laboratory knowledgeable about best practices for validation in the applicable discipline and do they have access to relevant documents? Is the client providing any information?
- Does the laboratory have a documented policy and procedures for validation of methods? Are they followed? The procedure may be generic or project-specific.
- Does the laboratory have procedures for assuring the quality of test results generated by test methods used in ad hoc/ non-routine testing?
- Who is assigned responsibility for validations? Are the staff trained in conducting validations and evaluating data packages?
- Is there a separation in the technical records between method development and validation?
- Is the validation documentation package complete?
- Is there evidence that the method has been successfully transferred to routine use, transferred to another laboratory or undergone some type of peer review, where appropriate?
- Is there a process to review performance data generated for methods in routine use to demonstrate to clients ongoing fitness for purpose?
- Is the method declared fit for purpose?

8 REFERENCES

8.1 Accreditation for Microbiology Laboratories EA-04/10 (European Co-operation for Accreditation). July 2002 rev 02.

8.2 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.

8.3 CITAC/Eurachem Guide, Guide to Quality in Analytical Chemistry. An Aid to Accreditation. Edition 2002.

8.4 Eurachem/CITAC Guide, Quantifying Uncertainty in Analytical Measurement. 2nd Edition. 2000 (QUAM:2000.P1).

8.5 EURACHEM Guide, The Fitness for Purpose of Analytical Methods. A Laboratory Guide to Method Validation and Related Topics. Edition 1.0, 1998. (see http://www.eurachem.ul.pt/guides/mval.htm).

8.6 European Communities 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 Communities, C(2002) 3044.

8.7 Guidelines for Single-Laboratory Validation of Analytical Methods for Trace-level Concentrations of Organic Chemicals. AOAC/FAO/IAEA/IUPAC Expert Consultation in Principles and Practices in Method Validation , Fajgelj, A, and Ambrus, A (Editors), Royal Society of Chemistry, 2000. (see www. iaea.org/trc, see pesticides, method validation).

8.8 ILAC G19:2002. Guidelines for Forensic Laboratories.

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8.10 Protocol for the Design, Conduct and Interpretation of Collaborative Studies. Pure Appl. Chem, 60(6), 1988, p 855-864.

8.11 Requirements for the use of single-laboratory validation for Codex purposes. Codex Alimentarius Committee. Codex Committee on Methods of Analysis and Sampling. 24th Session, November 2002.

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