CRITERIA FOR VALIDATION OF METHODS USED BY CHEMICAL LABORATORIES AND RELATED INDUSTRIES

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1. PURPOSE AND SCOPE

This document defines the concepts and processes of method validation and to provide technical requirements in order to facilitate a uniform approach to method validation. This document amplifies ISO/IEC 17025 requirements and lists SADCAS requirements applicable to the validation of methods in chemical laboratories.

These criteria are applicable to chemical testing of Coal, Oil, Petroleum, Metals, Minerals, Food, Pharmaceuticals, Water and related industries.

The following do not form part of this document:

- Sampling;
- Sample handling; and
- Transportation.

2. DEFINITIONS

2.1 **Accuracy -** The extent to which test results generated by the method and the true value agree. Accuracy can also be described as the closeness of agreement between the value that is adopted, either as a conventional, true, or accepted reference value, and the value found. Accuracy includes both trueness and precision.

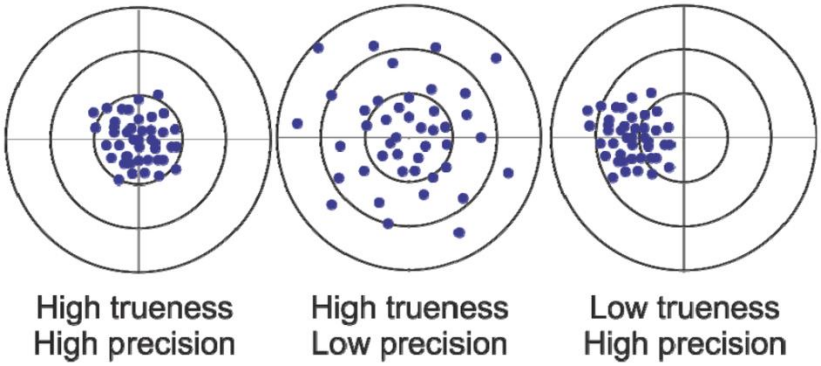
2.2 **Trueness** - The closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity values. Trueness is inversely related to systematic measurement error.

2.3 **Bias** - It is an estimate of systematic measurement error which is a component of measurement error that in replicate measurements remains constant or varies in a predictable manner. It varies inversely with trueness. The determination of bias relies on the comparison of the mean of the results from the candidate method with a suitable reference value. The reference value may be obtained from a matrix matched (as close as possible) certified reference material, by recovery experiments using spiked samples, by comparison with another validated (standard or reference) method or through Proficiency Testing participation.

2.4 **Precision** - the closeness of agreement between independent test results obtained by replicate measurements on the same or similar samples under specified conditions (how close the measured values are to each other). It is usually expressed as the standard deviation, relative standard deviation (RSD) or RSD% (coefficient of variation).

Figure 1- Graphic presentation of accuracy indicating the difference between trueness and precision.

From http://www.mdpi.com/2218-1989/2/4/1012/htm)



The specified conditions can be repeatability, intermediate precision or reproducibility conditions.

2.4.1. **Repeatability** - The conditions involve the same measurement procedure, same operators, same operating conditions, same measuring system and same location and replicate measurements on the same or similar objects over a short period of time.

2.4.2. **Intermediate Precision** - It can also be described as intra-laboratory reproducibility. The conditions involve the same measurement procedure, same location and replicate measurements on the same or similar objects over an extended period of time, but may include other conditions that can change. The changes can include new calibrations, calibrators, operators and measuring systems.
Note: Intermediate precision can most conveniently be obtained from data derived from the analysis of control samples run routinely over an extended period of time.

2.4.3. **Reproducibility** - The conditions include different locations, operators, measuring systems and replicate measurements on the same or similar objects. Reproducibility could be obtained from inter-laboratory studies.

2.5 **Linearity or linearity after a suitable transformation** e.g. quadratic fit - Ability of a method to obtain test results proportional to the concentration of the analyte within a given working range.

2.6 **Working range** - The range of an analytical method is the interval between the upper and lower levels of an analyte, including those levels that have been demonstrated to be determined with a suitable and defined level of precision, accuracy and linearity, using the method as written. The working range is normally expressed in the same units as the test results obtained by the analytical method.

2.7 **Limit of Detection (LOD)** - The lowest concentration of analyte that can be detected but not necessarily quantified under the stated conditions of the test. It is a point at which a measured value is larger than the uncertainty associated with it. Suitable approaches to estimate LOD can

be found in *B. Magnusson and U. Ornemark (eds.) Eurachem Guide: The Fitness for Purpose of Analytical Methods – A Laboratory Guide to Method Validation and Related Topics, (2nd ed. 2014). ISBN 978-91-87461-59-0.* www.eurachem.org.

2.8 **Verification** - Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

2.9 **Uncertainty of Measurement (Measurement Uncertainty)** - Parameter associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand.

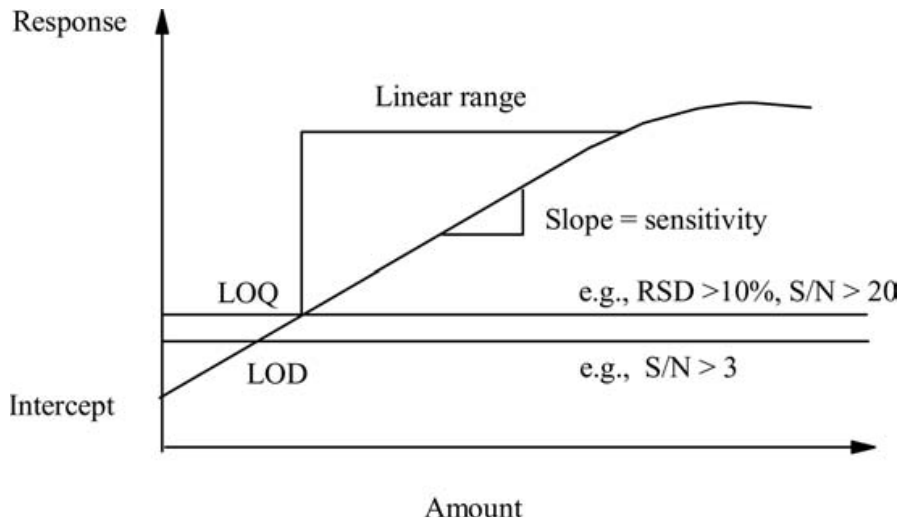
2.10 **Limit of Quantification (LOQ)** - The lowest concentration of analyte that can be determined with acceptable precision (and accuracy) under the stated conditions of the test.

2.11 **Sensitivity** - Capability of the method to discriminate between small differences of concentrations of analyte.

2.12 **Specificity/Selectivity** - The ability of a method to respond to a particular analyte of interest in the presence of possible interferences such as impurities, degradants and matrix effects.

2.13 **Robustness/Ruggedness** - Robustness of an analytical process is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters. Ruggedness provides an indication of the methods reliability during normal usage.

Figure 2 - The Definitions for linearity, range, LOQ and LOD displayed.



3. BACKGROUND

3.1 Method validation is the process of establishing the performance characteristics and limitations of a method and the identification of the influences which may change these characteristics and the extent to which they can be changed. It is also the process of verifying that a method is fit for purpose, i.e. for use for solving a particular analytical problem.

3.2 Verification refers to a process that provides evidence that the laboratory can achieve the performance characteristics given in a specific analytical method, especially accuracy and precision, and demonstrating that the method is suitable for the intended use. The extent and nature of such verification work depends on the needs of the customer, and the intended use.

3.3 Validation is always a balance between costs, risks and technical possibilities.

3.4 For clarification on when to perform validation or verification see Table 1. This Table has been adapted from PALCAN Guidance for the Validation of Test Methods.

Table 1 - When should methods be validated or verified?

Test method description	Validation or verification requirements
Standard published method.	Confirmation of the published performance characteristics (verification) in accordance with the requirements of ISO/IEC 17025
Standard published method plus additional documentation for optional steps.	Full validation may be required only if changes are made to the Standard method.
In-house developed method/ Lab Developed Method	Full validation (See Section 5).
Method published in the scientific literature without any performance data.	Full validation (See Section 5).
Methods published in scientific literature with performance data.	Confirmation of published performance characteristics (verification) but more likely full validation required.
Changes in implementation of previously validated methods i.e. changes to equipment, reagents, lab environment or staff.	Extent of validation will vary to demonstrate that the 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. the validation shall be extensive as is necessary to meet the needs of a given application or field of application.

Archived standard published or previously validated method that is reinstated.	Confirmation of previous performance characteristics (Verification).
Adhoc or special analyses (flexible scope accreditation)	Full validation of flexible scope accredited methods as required.
Commercial Test Kits – collaboratively tested, third party evaluation (e.g. AOAC).	Confirmation of published performance characteristics (verification) but validation may be required if and when changes are made or the matrices differ.
Commercial Test Kits – no performance data available, incomplete or not applicable.	Full validation.

4. PERFORMANCE CHARACTERISTICS AND CRITERIA OF A TEST METHOD

4.1 Performance characteristic "means functional quality that can be attributed to an analytical method". Examples of typical performance characteristics include but not limited to; selectivity, accuracy, trueness, recovery, precision, repeatability, reproducibility, limit of detection, limit of quantification, ruggedness and stability. When the laboratory is responsible for sampling, sub-sampling and transportation to the laboratory, sampling, sub-sampling and transportation must be part of the validation plan.

***Note*:** the validation should have taken into account the Reference Standards used and the purity and homogeneity of the sample.

4.2 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"..

5. VALIDATION PLAN

The scope of the method and its validation criteria must be defined early in the process. These include the following questions:

i) Purpose of measurement (what analytes should be detected and why?).

ii) What are the sample matrices?

iii) Are there interfering substances expected, if so, must they be detected and quantified?

iv) Are there any specific legislative or regulatory requirements?

v) How robust must the method be?

vi) Measurement scope (What are the expected concentration levels?)

vii) Are there specific equipment accommodation and environmental conditions that need to be considered?

viii) Which type of equipment should be used? Is the method for one specific instrument, or should it be used by all instruments of the same type?

ix) Method used for the sample preparation, sub-sampling, procedure and including instruments to be used.

x) Identification of performance characteristics:

- Accuracy
- Bias (systematic error)
- Precision
- Reproducibility
- Repeatability
- Linearity
- Working Range
- Limit of Detection
- Limit of Quantification
- Sensitivity
- Specificity
- Uncertainty of Measurement
- Robustness/Ruggedness

All of the above factors shall be addressed, however valid reasons shall be provided if a performance characteristic is not evaluated.

xi) Experimental design.

Within these approaches, laboratories should preferably follow the Eurachem Guide: The Fitness of Purpose of Analytical Methods. Other approaches may be followed provided that the laboratory can present scientific evidence that their approach is valid**.**

6. IMPLEMENTATION AND REVIEW

6.1 Analyze the data applying the appropriate statistical tools, e.g. Analysis of Variance (ANOVA tool, on Excel, for statistics), linear regression, t- test, f- test, etc.

Note*:* Ensure that conventions regarding use of significant figures and rounding data is applied before analyzing the data. Remember that when rounding data from chemical computations it may be necessary to carry one extra digit through all the computations to avoid rounding error. In rounding a number ending in 5, always round so that the result ends with an even number. For example: 5.45 will be 5.4; 5.35 will be 5.4; 5.55 will be 5.6.

Note: Units give dimensions to numbers therefore do not forget your measurement units.

6.2 Make a statement on fitness for purpose

6.3 Keep records of the validation, including raw data and other suitable evidence.

6.4 The final validation report shall contain conclusions, summaries of experimental data and calculations substantiating each of the applicable analytical performance parameters.

7. SUMMARY REPORT

7.1 The laboratory must have available for review a report, summarizing all method validation/verification for all methods used in the laboratory. The report shall include:

7.1.1 Reference to test method as validated/verified. 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).

7.1.2 Reference to the validation/verification procedure or plan used to generate the test method performance characteristics.

7.1.3 A summary of the test method performance characteristics and how these were calculated or defined. The raw data should also be available for review.

7.1.4 The test method performance criteria against which the characteristics were evaluated and whether or not the method is fit for purpose.

7.1.5 The intended use of the method.

7.1.6 Estimates of the uncertainty of measurement based on interpretive documents of the ISO GUM such as the Eurachem/CITAC Guide. When a whole-method approach is used, intermediate precision must be used as the basis.

7.1.7 The number of significant figures that should be reported for the result of the measurement depends on the uncertainty of the result; the uncertainty shall be rounded to two significant figures. Results shall be rounded to be consistent with the uncertainty given

7.2 If the method that is not a standard published method is used routinely, it is expected that 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.

7.3 SADCAS requires that all validation/verification data should be readily available in the laboratory for as long as the method appears on the schedule of accreditation.

8. RE-VALIDATION/RE-VERIFICATION

The laboratory is expected to continually prove that the validation/verification is still current through the quality control procedures that include the method's performance characteristics/parameters. Partial or full re-validation/re-verification may be considered when:

i) new instrument is introduced;

ii) new samples with new compounds or new matrices are introduced (Huber: 8.3);

iii) a new location with different environmental conditions is used (Huber: 8.3);

iv) new chemicals and/or reference standards are used (Huber: 8.3);

v) modifications are implemented due to analytical problems (Huber: 8.3);

vi) a review of quality control indicates an established method is changing with time;

vii) scheduled as per laboratory procedures;

viii) in the case of the method performance criteria falling outside the acceptance criteria (Huber 8.3).

Note 4: In the case where a new analyst is appointed to perform analysis, the laboratory is expected to ensure that the analyst is competent and meets the method's/relevant procedure's performance criteria.

9. REFERENCES

- B. Magnusson and U. Ornemark (eds.) Eurachem Guide: The Fitness for Purpose of Analytical Methods – A Laboratory Guide to Method Validation and Related Topics, (2nd ed. 2014). ISBN 978-91-87461-59-0. www.eurachem.org.
- ISO/IEC 17025 - General Requirements for the competence of testing and calibration laboratories. SADCAS TR 26-03 – Criteria for validation of methods used by Chemical laboratories in the Coal, Oil, Petroleum, Metals and Minerals, Food, Pharmaceuticals, water and related industries.
- PALCAN Guidance for the Validation of Test Methods. Can-P-1629. November 2006. Standards Council of Canada.
- Skoog, D.A. & West, D.M. Fundamentals of Analytical Chemistry, 99th Edition, 2014.
- SLR Ellison and A Williams (eds.) Eurachem/CITAC Guide: Quantifying Uncertainty in Analytical Measurement, (3rd ed. 2012). Available from www.eurachem.org.
- International Vocabulary of Metrology - Basic Concepts and Associated Terms (VIM), (2nd ed. 2008) by Working Group 2 of the Joint Committee for Guides in Metrology.
- GUM: Guide to the Expression of Uncertainty in Measurement. ISO, Geneva (1993).

- (ISBN 92-67-10188-9) (Reprinted 1995: Reissued as ISO Guide 98-3 (2008), also available from http://www.bipm.org as JCGM 100:2008). http://www.bipm.org as JCGM 100:2008)

- VAM Projects 3.2.1 Development and Harmonization of Measurement Uncertainty Principles Part (d) Protocol for Uncertainty evaluation from Validation data. V J Barwick and S L R Ellison. January 2000 LGC/VAM/1998/088.

APPENDIX – AMENDMENT RECORD

Revision status	Change			Approved by	Effective Date
	Page No.	Clause	Description of change		
Issue 1	-	-	-	SADCAS CEO	2018-03-24