ACCREDITATION UNIT

POLICY FOR VALIDATION OF TEST METHODS

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Purpose

The Accreditation Unit (JAS-AU) has set this document to ensure consistency in applying validation-testing procedures as a requirement for accreditation of testing and calibration labs.
In addition, the policy is intended to provide JAS-AU assessors with a tool in assessing laboratory performance as related to the quality of results they generate and report they issue.

Scope:

This document deals with the following subjects:

- Identification of methods, which require validation.
- JAS-AU requirements concerning data of validation.
- This document will help laboratories, accreditation bodies and regulatory authorities to apply and assess validation procedures used by the laboratories to ensure the performance of testing methods and quality of results generated and reported.
- Validation of computer software.

Authorship

This publication has been written by the Technical Committee, and approved by the Accreditation Director.

Official language

The text may be translated into other languages as required. The English language version remains the definitive version.

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Further information

For further information about this publication, kindly contact **JAS-AU**.
This document is also available at **JAS-AU website** where you can check updates directly.

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1. Introduction

Validation of an analytical laboratory method is the process by which it is established, by appropriate laboratory studies, that the performance characteristics of a method meets the requirements for the intended analytical application and it is fit for its intended use time after time in a consistent manner, and **shall be applied for non-standard methods, laboratory-developed methods and standard methods used outside their intended scope or otherwise modified.**

Verification on the other hand, is the process which is established by the appropriate laboratory to ensure the application of the validated method for its intended use and to ensure the performance and competence of its application in a consistent manner, **and** shall be applied for the standard method. Compliance with the requirements of validation and verification provides added assurance with regards to the quality and limitation of a reported test result.

Validation and Verification of the software are checking that a software system meets specifications and fulfills its intended purpose.

Validation of the drug manufacturing, documenting that a process or system meets its pre-determined specifications and quality attributes.

Users of this policy should note that although there are many publications and methods for validating and verifying different methods, but no one method is universally agreed depending on the studied matrix. The number of repeated testing (independent replicates) required to study method characteristics and definitions of some of the terms used in method validation vary, thus, it is **JAS-A**U requirement that the definitions and terms used by laboratories should adhere to those used in this policy.

Validation of test methods serves to understand and control the testing method. Including the calculation of combined uncertainty, linearity, detection limits, range, the precision and bias.

2. Definitions

The definitions used in this document are based on applicable Eurochem documents and other documents listed in the Reference section.

3. Responsibility

a- It is the responsibility of JAS-AU assessors to evaluate the compliance of the laboratories with this Policy.
b- Laboratories heads are responsible for ensuring compliance with this policy.

4. Policy

4.1 Verification:

National and International Standards Methods adopted from reputable technical organizations are not required to be validated when used without any changes affecting the test results, it needs only verification of the applied method to ensure that it fits the intended use.

It is worthwhile to mention that although such methods **do n**eed not **to b**e validated. The requirement for a method to be valid is for it to be a recognized standard or a validation report that confirms that its performance is inline with the requirements.

The testing or calibration laboratory should confirm some of the parameters such as precision and bias as defined in the valid method and used for the **evaluation** of the method uncertainty.

A partial validation is verification. The laboratory **shall** show that the characteristics defined in the validation are achieved when the test is performed in the laboratory.

The verification **shall** prove that the standard method is applicable in the laboratory in a repeatable and/or traceable manner. Verification studies may require reduced number of repeated testing (independent replicates) compared to validation study.

Validation and verification studies need to include the necessary tests selected for a specific study and may have to include all of the validation characteristics.
Tests are selected in accordance with the needs for which a method is “intended to be used” -in this context, the terms validation and verification are synonymous.

4.2 Validation:

The stated purpose of validation is to confirm that the methods are fit for the intended use **as** a result, the validation shall be as extensive as is necessary to meet the need of the given Application for field of application also the laboratory shall record the results obtained, the Procedures used for the validation, and a statement as to whether the method is to fit for the Intended use.

Once a method is modified, updated or introduced as a new one within the given scope, it **shall** be validated before it can be considered as being included in the scope of accreditation to ensure that it is fit for the intended use.

Procedures and responsibilities for development, implementation and validation of such methods should be described in detail within the **management** documentation. Flow charts are useful tools to achieve these goals. The responsible **personnel** will have to state the minimum quality requirements ((Validation Protocol which describe procedure of validation and accepted criteria for each test) before starting the process of validation and implementation, or even better, before starting the whole development process.

Authorized and experienced **personnel shall** take the responsibility for modification, development and implementation of new or revised methods.

Assessors shall be able to judge whether the applied procedures will provide the results needed to define the quality of an individual method with view to its field of application and the kind of products tested.

Modifications and **updates** of test methods or development activities including all the underlying results and other relevant data (e.g. results of validation) **shall** be controlled and maintained on record. This data shall be available on request for the Accreditation Body, which has to check it during a surveillance visit, a reassessment or on request.
The responsible **personnel** (including those responsible for management **system)** shall regularly review the modified, revised or newly developed methods.

Procedures and responsibilities linked to the development or revision of accredited methods shall be reviewed periodically by the responsible management taking into account the results of internal and external quality control. Records of these review activities must be available to the Accreditation Body.

The laboratory shall authorize personnel to perform development, modification, verification and validation of methods

4.3 Type of Test Methods under Scope of Accreditation that a validation is required for include the following:

4.3.1 Non standard and "In-House" methods: all in-House methods shall be validated using the criteria in relevance to the intended use.

4.3.2 Standards methods that are modified by the laboratory and may impinge the quality of the results.

Modification may include modification of equipment **and** software, diluents , matrix, reference materials and standards, media, control parameters such as time **and** temperature, test environment, addition or omission of steps, modification in samples handling, changes in calculations etc).

4.3.3 Standard methods used outside the limits of approved scope.

The extent of a validation or re-validation required for circumstances mentioned in points 4.3.1-4.3.3 are dependent upon the nature of the data, which has been determined as essential to demonstrate fitness for the intended use.

The extent required should be assessed based on sound scientific data and/or rational. The laboratory shall document the rational for omission and inclusion of the specific validation characteristic of the entire spectrum of characteristics to be validated in a quantitative analytical method includes some or all the listed performance parameters; which are applicable:

- **Accuracy and recovery – Closeness of agreement between a test result and the accepted reference value, is calculated as the percentage of recovery by the assay of the known added amount of analyte in the sample, or as the difference between the mean and the accepted true value, together with confidence intervals.**
- **Precision – Consistency of measurements using same method by same operator and same instrument.**
- **Working Range – The working range is predefined by the purpose of the method and may reflect only a part of the full linear range which covers the upper and lower values of a particular analyte in a sample capable of being detected by a method with good accuracy and precision.**
- **Repeatability – intra-assay precision; measurements by one person or instrument on the same item (and over a short time interval).**
- **Reproducibility – replication of data by another examiner using different instrument and different days.**

- **Robustness/Rigidness – efficacy of method to small variations in parameters.**
- **Specificity & Selectivity – ability to detect analyte in presence of other components.**
- **Linearity; a directly proportional relationship between the method response and concentration of the analyte in the matrix over the range of analyte concentrations of interest.**
- **Limit of detection; lowest analyte concentration that can be detected and identified with a given degree of certainty.**
- **Limit of quantification; the lowest concentration of the analyte that can be determined with an acceptable repeatability and trueness.**
- **Sensitivity; the lowest analyte concentration that can be measured with acceptable accuracy and precision (i.e., LLoQ)"Uncertainty**
- Or any other relevant performance indicators

4.4 In the context of this document, the intended use may be interpreted as below:

- A method intended to demonstrate the absence of a given contaminating measurand / analyte should be validated for LOD (Limit of Detection) and does not require studies such as linearity.
- A method used to generate results upon which the **customer** of the result is likely to act, should specify the order of magnitude of useful values to be used for the measurand subject to the validation studies, i.e. the quantitative order of magnitude of the values of interest - this knowledge, in addition to its essence for the planning of the validation, will determine the methods' fitness or lack of it. (The validation acceptance criteria should address relevant values suited for the intended use).
- Under optimal conditions, such as in cases of introduction of a new laboratory method, validation should be designed and performed prospectively (prior to introduction of the method for use to provide the client with test results).

  It should be emphasized that validation prior to use of the method is recommended as the first step however, one should repeat this validation as an on-going activity to confirm the link between the performance of the laboratory and the initial tests

4.5 Non-validated method that has been used in the past should be subjected to validation. This validation should be based on past relevant data, provided the data is judged to be scientifically valid, relevant and that all method changes throughout the period from which the data has been derived from are fully traceable. Regardless of the type of validation, a protocol and associated approved report are obligatory.

4.6 Verification of previously validated methods. The laboratory only needs to verify that their operators using their equipment in their laboratory environment can apply the method satisfactorily. Full validation is required if a laboratory has reason to significantly modify a standard method, for example, use a different extraction solvent or changing the instrument such as using HPLC instead of GLC for determination. Additional validation should be considered if the validation data for a standard method is not available to the laboratory or the laboratory needs to apply specifications more stringent than those for which the standard method has been validated. Minor modifications to previously validated in-house methods, for example, using the same type of chromatographic column from a different manufacturer, should also be verified. The key parameters to consider in the verification process will depend on the nature of the method and the range of sample matrices likely to be encountered. The determination of bias and precision are minimum requirements. Ideally the laboratory will be able to demonstrate performance in line with method specifications. If not, judgment should be exercised to determine whether the method can be applied to generate test results fit for purpose.

4.7 With regards to number of repeated testing (independent replicates) required for the study of validation characteristic, it should be determined based on sound statistical pre validation data (the more, the less uncertain the test results are).

4.8 Instead of a validation study JAS-AU management shall accept scientific data, which is generated by a laboratory during the routine conduct of statistical quality control tests (control charts data) and other laboratory Control Testing Program data. Such data, when presented in an un-ambiguous and comprehensive manner and addresses validation parameters of interest, shall be considered as satisfying JAS-AU validation requirement provided that the Test Method is identical to the procedure which otherwise would be required to be validated. Laboratories engaged in planning these activities should consider validation issues so as to avoid redundant work.

4.9 The laboratory shall document and follow their validation and verification procedures. The policy should also include a policy for re-verification. As a minimum, re-verification is required when:

- The results of the validation do not conform to its pre determined acceptance criteria.
- The post validation calibration indicates that an instrument calibrated prior to the validation study conduct shifted out of its calibrated state during the validation study to such an extent that it casts doubt regarding the validity of the data generated in the study.
- Once changes are made to validated non-standard methods.
- Upon testing site change, including equipment, or a major environmental change.
- Methods, which are not used on a routine basis, including standard methods.
- Introduction of new lot/batch of a reference standard.

4.10 In order to assure that a validated method remains in a controlled state, the laboratory shall implement periodic re-verification plan or observe and control the method in an "on going" fashion by the usage of appropriate statistical quality control calculation and charting techniques.

4.11 For method associated with software validation; (ISO/IEC 17025:2017 (E) **7.11.2** **JAS-AU** requires that computer software, developed by the user **and** used in the performance of a laboratory method subject to validation, **shall** be sufficiently documented so as to provide evidence that it is suitably validated as being adequate for use for its intended purpose.

The laboratory information management system(s) used for the collection, processing, recording, reporting, storage or retrieval of data shall be validated for functionality, including the proper functioning of interfaces within the laboratory information management system(s) by the laboratory before introduction. Whenever there are any changes, including laboratory software configuration or modifications to commercial off-the-shelf software, they shall be authorized, documented and validated before implementation.

JAS-AU consider commercial off the shelf software in general use within their designed application range to be sufficiently validated.

4.12 Laboratories engaged in a validation study should use well-characterized Standard Reference Material, which is maintained and used in accordance with written instructions. The material should be traceable to a national or internationally recognized Certified Reference Material (CRM) when available or Reference Standard (as per ISO 17034:2016) with a certificate of analysis

4.13 Validation may be contracted out, provided it is followed by verification by the laboratory to ensure that the methods fit its intended use.

4.14 Verification cannot be contracted out –it must be conducted on site, under the responsibility of the laboratory, which intends to run the test under routine use and by the personnel intended to run the test method routinely.

4.15 The test method subject to the validation study shall be documented and approved. The method shall not be changed throughout the validation study or after the study without duly approved, documented change control activity. Such changes may require revalidation.

4.16 Validation **shall** be designed as planned. A detailed validation protocol **shall** include the acceptance criteria for approval by the laboratories' authorized personnel. Acceptance criteria should include pre and post validation calibration results. For a successful study, both calibrations should demonstrate that the equipment and the instruments have remained in a calibrated state. (i.e.: demonstrating that drift, if apparent, between the reference standard and the calibrated instrument is such that it has negligible effect on the method), If this was not the case, a repeated validation should be performed.

4.17 Personnel engaged in the validation procedures should undergo a thorough training. Such training should be **recorded**.

4.18 Validation data shall be signed by the responsible personnel

4.19 The desired combined uncertainty should be set as part of the acceptance criteria. Precision value of the method (considered to be the main contribution to the measurement uncertainty) should never exceed the desired combined uncertainty.

4.20 The validation report should include individual test results in addition to other numerical expressions as needed. The provision of a table comparing results and evidence for achieving the acceptance criteria, which were set up in the protocol, is an obligatory component of all validation reports.

4.21 All raw data shall be signed and approved by authorized personnel, secure and should include all of the results, including those out of specifications.

4.22 The lab should evaluate the adequacy of the test method under consideration and assure that expanded uncertainty has been calculated for the validated method.

The laboratory shall retain the following records of validation:

a) The validation procedure used;

b) Specification of the requirements

c) Determination of the performance characteristics of the method;

d) Results obtained;

e) A statement on the validity of the method, detailing its fitness for the intended use.

5. References

5.1 Harmonized guidelines for single Laboratory validation of methods of analysis. (IUPAC Technical Report), 2002, Pure Appl. Chem, Vol: 74, No 5, pp: 835-855.

5.2 Validation of Bio-analytical method, Shah. B *et al*., 1998. Pharmaceutical Research, Vol: 8, No 4.

5.3 Euro Chem Guide, The fitness for analytical method, 2014

5.4 Guidance for Industry, Bi-analytical method validation, FDA, 2001.

5.5 PALCAN guidance for the validation of test methods CA-P-1629 NOV.2006

5.6 Guidelines for the validation and verification of quantitative and qualitative test methods Published by the National Association of Testing Authorities, Australia (NATA) 201**8.**