



ACCREDITATION UNIT

POLICY FOR METHOD VALIDATION IN MEDICAL LABORATORIES

Purpose

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

Scope:

This document addresses the following subjects:

- Identification of methods which require validation.
- **JAS-AU** requirements concerning validation data.
- This document provides general **requirements** to laboratories, accreditation bodies and regulatory authorities on validation steps that laboratories **shall** follow to ensure acceptable performance of testing methods and consequently the quality of results generated.
- Validation of computer software.
- Validation of any other elements involved affecting the testing process
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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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1. Introduction

Method validation is an important practice in the field of medical tests, it helps to demonstrate that methods used are fit for its purpose. Clause 5.5.1.1 of the international standard ISO 15189:2012 indicates that the laboratory ***shall*** select examination procedures which have been validated for their intended use. In addition, clause 5.5.1.2 indicates **that** Validated examination procedures used without modification ***shall*** be subject to independent verification by the laboratory before being introduced into routine use.

Although there are many publications and methods on the validation and verification of different laboratory methods and systems, no one method is universally agreed upon. The recommendations on the specimens/replicates needed to study method characteristics and the definitions of some of the terms used in method validation do vary across references, thus, it is **JAS-AU** requirement that the definitions and terms used by laboratories **shall** adhere to those used in this policy whenever applicable.

2. Definitions

The definitions used in this document are based on international vocabulary of Metrology (VIM), 3rd **Edition**: 2012, and other documents listed in the references section:

(2.44 – VIM: 2012) Provision of objective evidence that a given item fulfills specified requirements.

NOTES:

- 1- When applicable, measurement uncertainty should be taken into consideration.
- 2- The item may be, e.g. a process, measurement procedure, material, compound, or measuring system.
- 3- The specified requirements may be, e.g. that a manufacturer's specifications are met.
- 4- Verification should not be confused with calibration.
- 5- In chemistry, verification of the identity of the entity involved, or of activity, requires a description of the structure or properties of that entity or activity.

Verification:

Confirmation, through provision of objective evidence, that specified requirements **have been fulfilled.**

Validation:

Confirmation, through the provision of objective evidence, that the requirements **for a specific** intended use **or application have been fulfilled.**

3. Responsibility

- a- It is the responsibility of **JAS-AU** assessors to evaluate the compliance of the laboratories with this Policy.
- b- Laboratory Director **is** responsible for ensuring compliance with this policy.

4. Policy

4.1 Validation:

The stated purpose of validation is to confirm that a method is fit for its intended use. As a result, the validation shall be as extensive as necessary to meet the need of the given application. Validation must cover all aspects of the method and recruit adequate number of samples as recommended in the published and adopted validation protocol.

The laboratory shall validate examination procedures derived from the following sources:

- a) non-standard methods;
- b) laboratory designed or developed methods;
- c) standard methods used outside their intended scope;
- d) Validated methods subsequently modified. Modification may include modification of: equipment and software, reagents, diluents and matrix, reference materials and standards, media, control parameters such as time and temperature, test environment, addition or omission of steps, modification in sample handling, changes in calculations etc.

The laboratory shall document the protocol/procedure used for the validation, the raw data and records of the results obtained from validation studies must be kept on file, and a statement as to whether the method is fit for the intended use or not shall be written in the validation report. This data shall be available on request for the Accreditation Body, which has to be checked during **the assessment** Visit or upon request.

Once a method is modified, updated or introduced as a new method within a given scope, it **shall** be validated before it can be considered as being included in the scope of accreditation.

The laboratory director or designee **shall** review the validation protocol, raw data, findings and the conclusion of whether validation is acceptable or not.

An authorized **personnel shall** take the responsibility for modification, development and implementation of new or revised methods and under the supervision of the laboratory director.

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

The responsible personnel (including those responsible for quality management) shall regularly review the modified, revised or newly developed methods. Procedures and responsibilities linked to the development or revision of validated 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 **shall** be available to the Accreditation Body.

4.2 Performance characteristics evaluated during method validation

The extent required should be assessed based on 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. Characteristic to be validated in a Quantitative analytical method may include some or all the below listed performance parameters applicable to the method in question;

- Trueness
- Accuracy
- Precision (repeatability & reproducibility)
- Recovery
- Specificity **and** Selectivity
- Linear and working range
- Limit of detection

- Limit of quantification
- Sensitivity
- Robustness/Rigidness
- Interferences
- Carry over
- Or any other relevant performance characteristic

4.3 Verification:

The intended purpose of verification is to confirm, through obtaining objective evidence that the performance claims reported by the manufacturer for the examination procedure/system have been met in-house using the named laboratory resources and can thus be put into service for its intended use. The performance claims for the examination procedure confirmed during the verification process shall be those relevant to the intended use of the examination results.

The laboratory shall verify the performance of verified/validated examination procedures if there is an important change such as introduction of a new piece of an existing instrument model, relocation of equipment etc.

Commercially available standard methods from reputable manufacturers or those adopted from reputable technical organizations may not need to be validated when used without any changes affecting the test results. Such methods are usually well validated by the manufacturer and were subjected to approval by regulatory bodies such as FDA or CE or validated procedures implanted from an accredited expert laboratory. However, verification for such methods is needed given that the original protocols are used exactly as described; any change of conditions (eg, reduction of reagent volumes) would invalidate the performance criteria and lead to a need for validation and remains the responsibility of the testing laboratory.

The laboratory **shall** be able to demonstrate that the characteristics set by the manufacturer are achieved when the test is performed in the laboratory.

As a minimum, the testing laboratory **shall** provide evidence that key parameters of the method including accuracy, precision, analytical measuring range, limits of detection/quantification, linearity and reference limits are verified. Reportable range should also be defined. Although it

is preferred that testing laboratories verify parameters such as specificity and interferences, manufacturer published data may be acceptable.

Data on precision and bias is also needed for the estimation of the method uncertainty.

Validation/verification material used should cover all applicable matrices such as serum, urine, CSF etc.

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

- A method intended to demonstrate absence of a given analyte should be validated for LOD (Limit of Detection) and does not require studies such as linearity.
- 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 **patient** 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 periodically as defined in laboratory policies to confirm the link between the ongoing performance of the laboratory and the initial validation results.

4.5 Non-validated method that has been used in the past **shall** be subjected to validation. This validation **shall be** based on past relevant data, provided the data is judged to be scientifically valid, relevant and 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 With regards to number of repeated testing (independent replicates) required for the study

Of validation characteristic, the laboratory director or designee shall decide on this, the decision should be based on sound science, published data, experience and performance requirements; it is the responsibility of the laboratory to provide evidence that the tests provided are reliable, and that the performance claims are correct.

4.7 Instead of a validation study, **JAS-AU** accepts scientific data generated by a laboratory during the routine conduct of testing/statistical quality control (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 satisfying to **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. This approach should not be applied to routine testing and may be applied to specific circumstances where obtaining validation samples is extremely difficult.

4.8 The laboratory shall document and follow their validation and verification procedures. As a minimum, re-verification is required when:

- The results of the verification/validation do not conform to its pre-determined acceptance criteria.
 - 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.
 - Key parameters such as linearity, limit of detection etc. should be verified every six months.
- Introducing of new lot/batch of a reference standard

4.9 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 “ongoing” fashion by the usage of appropriate techniques.

4.10 For method associated with software validation; ISO15189:2012 **and JAS-AU** require 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.

JAS-AU shall consider commercial off the shelf software in general use within their designed application range to be sufficiently validated however verification is still needed.

When interfacing laboratory instruments to information system, the laboratory **shall** validate the data transfer process and ensure accurate transfer of results.

Whether or not a method by itself is required to be validated, laboratory software re-configuration and modification should be validated. When the software is used for

calculation leading to result generation, such calculations must be verified for accuracy by at least comparing it to manual calculation.

- 4.11** Laboratories engaged in a validation study should use well-characterized Standard Reference Material, which are maintained and used in accordance with written instructions. The material should be traceable to a national or internationally recognized Reference Material or non-certified with known target values when available or Reference Standard (as per ISO **17034**) with a certificate of analysis (CoA).
- 4.12** Validation may be contracted out, provided it is followed by verification by the laboratory to ensure that the methods fit their intended use on site.
- 4.13** Verification cannot be contracted out –it **shall** 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. The lab shall use the same Equipment, the same materials and in the same environmental conditions
- 4.14** 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 otherwise the method considered void and will require revalidation / revivification, however such changes **shall** be documented.
- 4.15** Validation **shall** be designed as planned. A detailed validation protocol **shall** include the acceptance criteria for approval by the laboratories' authorized personnel.
- 4.16** Personnel engaged in the validation procedures should undergo a thorough training. Such training **shall** be documented.
- 4.17** The validation report **shall** include individual test results in addition to other numerical expressions as needed.
- 4.18** All raw data **shall** be secured and **shall** include all of the results, including those out of acceptable limits.
- 4.19** Validation report and related raw data shall be kept by the lab and be readily available for assessment purposes as long as the test method is used in the lab and 5 years after it's withdraw from use.

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