Validation and verification of examination procedures in medical laboratories

A practical proposal for dealing with the ISO15189:2012 demands

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Working group – Verification & Validation of Examination Procedures
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1 Introduction

The International Standard, ISO 15189:2012 – ISO 15189 in short – specifies requirements for competence and quality for medical laboratories. Medical laboratory services form an essential link in the chain of services needed for patient care. The services of medical laboratories include handling examination requests, patient preparation, patient identification, collection of samples, transportation, storage, processing and examination of clinical samples. In addition to these technical aspects, laboratory services include consultancy offered to the requesters – advising on the choice of tests to be used, dealing with measurement uncertainty and, finally, interpreting results. Over the years, the ISO 15189 has been clear in many statements on maintaining the desired quality system and improving the quality of the output of medical laboratories.

However, the demands of ISO15189 for the examination procedure validation and verification (sections 5.5.1.1 – 5.5.1.3) are not more than a framework, lacking sufficient details in practical use. The board of the Netherlands Society for Clinical Chemistry and Laboratory Medicine (abbreviated NVKC in Dutch) therefore assigned a special working group to supplement ISO 15189 with a Dutch guideline on validation and verification for the members of the Netherlands society. The document presented here is a slightly adapted version of this Dutch guideline, and intended as a draft for an international guidance document on validation and verification of examination procedures complying with ISO 15189.

Although this present document is primarily meant for application in clinical chemistry, it may also be useful and relevant for other disciplines in medical laboratories, such as clinical pharmacy, medical microbiology and medical immunology.

2 Scope

This document will deal with the following key questions:

- What is the difference between validation and verification of examination procedures?
- In which cases should a validation of an examination procedure be performed and in which cases a verification?
- What performance characteristics should be evaluated?
- What validation, verification or modification of examination procedures should be documented?
- What implementation procedures should be followed?

This document is valid for examination procedures used for human diagnosis or follow-up examination in medical laboratories. Measuring equipment such as analyzers are not taken into consideration, at least not where installation and technical-operational aspects of such measuring equipment are concerned. The document focuses essentially on quantitative measuring of a measurand (see Terms and definitions –section 5) in a biological matrix; however, it may also (partly) apply to qualitative analysis.

3 Normative references

- ISO 15189:2012 Medical laboratories – Requirements for quality and competence
- ISO 22870:2006 Point-of-care examination (POCT) – Requirements for quality and competence
- Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. Official Journal L 331 , 07/12/1998 P. 0001 - 0037

4 Background documents

- Clinical Laboratory Improvement Amendments (CLIA), Final rule 2013 and Brochures

- CLIA Brochure #2 Verification of Performance Specification
- ISO 15193:2009, In vitro diagnostic medical devices; Measurement of quantities in samples of biological origin – Requirements for content and presentation of reference measurement procedures
- Clinical Laboratory Standards Institute, Evaluation protocols: EP5, 7, 9, 10, 12, 14, 15, 17, 23, 26 and 28
- ISO/IEC 17000, Conformity assessment —Vocabulary and general principles
- ISO/IEC 17025:2005, General requirements for the competence of examination and calibration laboratories
- ISO/IEC Guide 2, Standardization and related activities — General vocabulary
- JCGM 2000:2012 International Vocabulary of Metrology – Basic and general concepts and associated terms (VIM), 3rd edition of the 2008 version with minor corrections
- Sandberg S, Fraser C, Horvath AR, Jansen R, Jones G, Oosterhuis W, et al. Defining analytical performance specifications: consensus statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem Lab Med 2015;53:833–5. (Milan conference 2014)

5 Terms and definitions

Most definitions are taken directly from the International Vocabulary of Metrology (VIM), some contain additional information for clarification in the context of this document.

5.1 Acceptance criteria

Specific requirements with respect to performance characteristics, depending on the intended use of the examination procedure. Acceptance criteria, stated as performance characteristics in ISO 15189, are usually expressed as a measure of quantity.

5.2 Analyte

Component or chemical entity that can be measured.
Note: The difference between analyte and measurand is explained in the following example: ALAT is an enzyme (the analyte) that is measured indirectly, while the ALAT activity in serum, measured using the IFCC method, is the measurand.

5.3 Intended use

The “intended use” of a medical examination procedure comprises the clinical condition and/or the issue prompting the examination procedure, as well as the manner in which the examination procedure, including preparation, is to be carried out. The acceptance criteria and the intended use are connected. Changing the intended use for specific situations will possibly alter the acceptance criteria.

5.4 Measurand

Quantity intended to be measured. The substance to be measured, the examination procedure and the matrix shall be defined: for example, D-glucose in blood serum using the hexokinase method (see also section 6.2).

5.5 ISO 15189

Refers to the original ISO15189:2012 (in English).

5.6 Examination procedure

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: ISO 15189 also mentions “Standard examination procedure”. This is an examination procedure carrying the status of “standard”, for instance, a reference method or a professional society’s detailed description of an examination procedure (measurement of an enzyme using the IFCC method, for example).

5.7 Performance characteristics

Established quality characteristics of an examination procedure for which, after substantiation and depending on the intended use, acceptance criteria can be assigned. Subsequently, these quality characteristics shall be examined by means of verification or validation. A performance characteristic comprises both magnitude and result.

5.8 Reference interval

The biological reference interval is a defined interval for the distribution of values derived from a biological reference population.

5.9 Reference value

The term “reference value” is reserved for the value of a reference material. Do not use the term “reference value(s)” to express “reference interval”.

5.10 Validation of an examination procedure

Demonstration via objective evidence that a **new or modified** examination procedure from one’s own working environment (or laboratory) is appropriate for a specific intended use in medical diagnostics, and that it complies with the relevant acceptance criteria as described by the medical laboratory. See Recommendation II for clarification of “new or modified” examination procedures.

5.11 Verification of an examination procedure

Confirmation via objective evidence that an **already validated** examination procedure from one’s own working environment (or laboratory) is appropriate for a specific intended use in medical diagnostics, and that it complies with the acceptance criteria as described by the medical laboratory.

5.12 Validation/verification plan

A defined and authorized protocol that describes the manner in which the validation/verification shall be performed and by whom it shall be performed.

5.13 Validation/verification report

Well-ordered documentation of the evidence and results on which the conclusion of the validation/verification is based.

6 Validation and verification

In compliance with ISO15189, examination procedures shall be subjected to independent validation or verification by the medical laboratory prior to being introduced. Which performance characteristics and acceptance criteria are relevant for validation or verification shall, depending on the intended application, be established in the validation or verification plan in order to objectively assess if the examination procedure is appropriate for the intended use.

I Recommendation

The laboratory shall use only examination procedures that have been validated or verified by the laboratory for the intended use.

6.1 Validation or verification

In practice, there is frequent confusion about the choice between either validation or verification. This depends on the availability of reliable and valid data on the performance characteristics of the envisioned examination procedure. The data can, for example, be supplied by the diagnostics supplier (CE or FDA marketed), or be taken from peer-reviewed texts/journals or from validation/verification data from other accredited laboratories.
The laboratory collects reliable and valid data on the performance characteristics and examines the data to ascertain if the acceptance criteria have been met. If so, verification of relevant performance characteristics is sufficient. If the performance characteristics are either not available or do not meet the acceptance criteria, the laboratory shall collect its own data (validation).
Therefore, for example, it may occur that for procedures validated elsewhere, verification can be sufficient for precision, trueness and decision limit procedures, but that supplemental validation of the sample´s stability will be necessary.

6.1.1 Validation of examination procedures

ISO 15189 emphatically states a number of categories of examination procedures to be validated. The term “methods” mentioned in ISO 15189 complies with the new term, “examination procedures”.

II Recommendation

The laboratory shall validate examination procedures derived from the following sources:
a) non-standard examination procedures
b) laboratory-designed or developed examination procedures
c) validated examination procedures used outside their intended use
d) validated examination procedures subsequently modified

Recommendation II further explained:
The non-standard procedure named under a) is named in ISO 15189, but in practice always refers to the procedure named under b) or c). In c), a “validated examination procedure” is considered equivalent to the terminology “standard method” named in ISO 15189.
Part of the validation process is the objective establishment (through measurement) of the relevant performance characteristics. In the above-mentioned situations, either the performance characteristics are not established according to ISO 15189, or the examination procedure has been modified in such a way that these performance characteristics are, according to ISO 15189, not automatically valid for the modified examination procedure.

6.1.2 Verification of examination procedures

The performance characteristics of the examination procedure evaluated during the verification process shall be relevant for the intended use of the results of the examination.
If all the relevant performance characteristics are both available and valid for one’s own laboratory, the examination procedure can be subject to verification instead of validation.
Here, “valid” means that the data have been obtained under documented similar conditions as those for the intended use. The laboratory shall have information available from the manufacturer/developer of the examination procedure, or examination results from reliable independent studies in order to be able to confirm the known performance characteristics of the examination procedure. When more than one device is used to measure the measurand, the correct operation of each individual device shall be verified.

III Recommendation

Examination procedures that, on the basis of available documentation, do not necessarily have to be validated shall at least be verified for the relevant performance characteristics.

IV Recommendation

If evidence from a validation performed elsewhere is incomplete, verification is insufficient and a supplemental validation in one´s own laboratory shall be necessary.

V Recommendation

When using more than one analyzer for the same measurand, an appropriate verification of each individual device shall be performed applying the appropriate acceptance criteria.

6.1.3 Modified examination procedures

If an examination procedure is modified after validation or verification, the effect of such a modification shall be taken into consideration and evaluated (documented motivation). A risk analysis may be used here. If applicable, a new validation or verification shall be performed, as described in section 6.1.1 or 6.1.2.

VI Recommendation

If an examination procedure is modified, it shall be taken into consideration and documented if there are potential/relevant consequences for the performance characteristics and, if so, what these consequences are.

VII Recommendation

When an examination procedure is modified with respect to the documented motivation, a (supplemental) validation or verification shall be performed.

6.1.4 Verification based on performance characteristics for examinations without acceptance criteria

Performance characteristics from an "open" evaluation study, in which no acceptance criteria have been previously established, are permitted to be confirmed in a verification. To be acceptable, these performance characteristics should have been established in a well-documented way comparable to a validation study, and should be valid for the intended use. For example, original publications on examination procedures are seldom set up primarily for validation examination, although they may deliver useful data.

In the verification plan, the available performance characteristics can be assessed for compliance to the acceptance criteria established by staff with the appropriate authority. The data from the original study are considered here as being comparable and offering an alternative to a formal validation study. In an additional verification it shall be confirmed that the performance characteristics relevant to the intended use meet the acceptance criteria.

6.2 Establishing a validation or a verification plan

For both validation and verification, performance characteristics shall be assessed against the acceptance criteria. These acceptance criteria are pre-established and justified in the validation and verification plans, respectively. Besides the **acceptance criteria**, the measurand, intended use and the manner of examining shall have to be established; furthermore, the investigators and the staff member with the appropriate authority shall be identified.

Particularly for validation of a (self-developed) examination procedure, it is essential to clearly define the measurand. Describing the measurand requires knowledge of the component or chemical entity (analyte), the matrix and the condition of the analyte, as well as the characteristics of the examination procedure used. This plays a crucial role, for example, in immuno-chemical examination procedures.

VIII Recommendation

Validation/verification shall take place according to a pre-established and pre-authorized validation/verification plan, comprising at least the following elements:
1) intended use of the examination procedure
2) documentation of the measurand
3) selection of the relevant performance characteristics
4) acceptance criteria valid for the intended use
5) examination method
6) identity of investigators and competent authorizer(s)

The laboratory shall document the procedure used for the validation and record the results obtained. A staff member with the appropriate authority shall assess validation results and compile the assessment report.

IX Recommendation

The verification/validation plan shall be authorized by staff with the appropriate authority.

6.3 Flowchart for various scenarios

The workflow for the various scenarios for which validation or verification is necessary is presented schematically in Figure 1. See Annex 1 for a detailed description of the workflow.

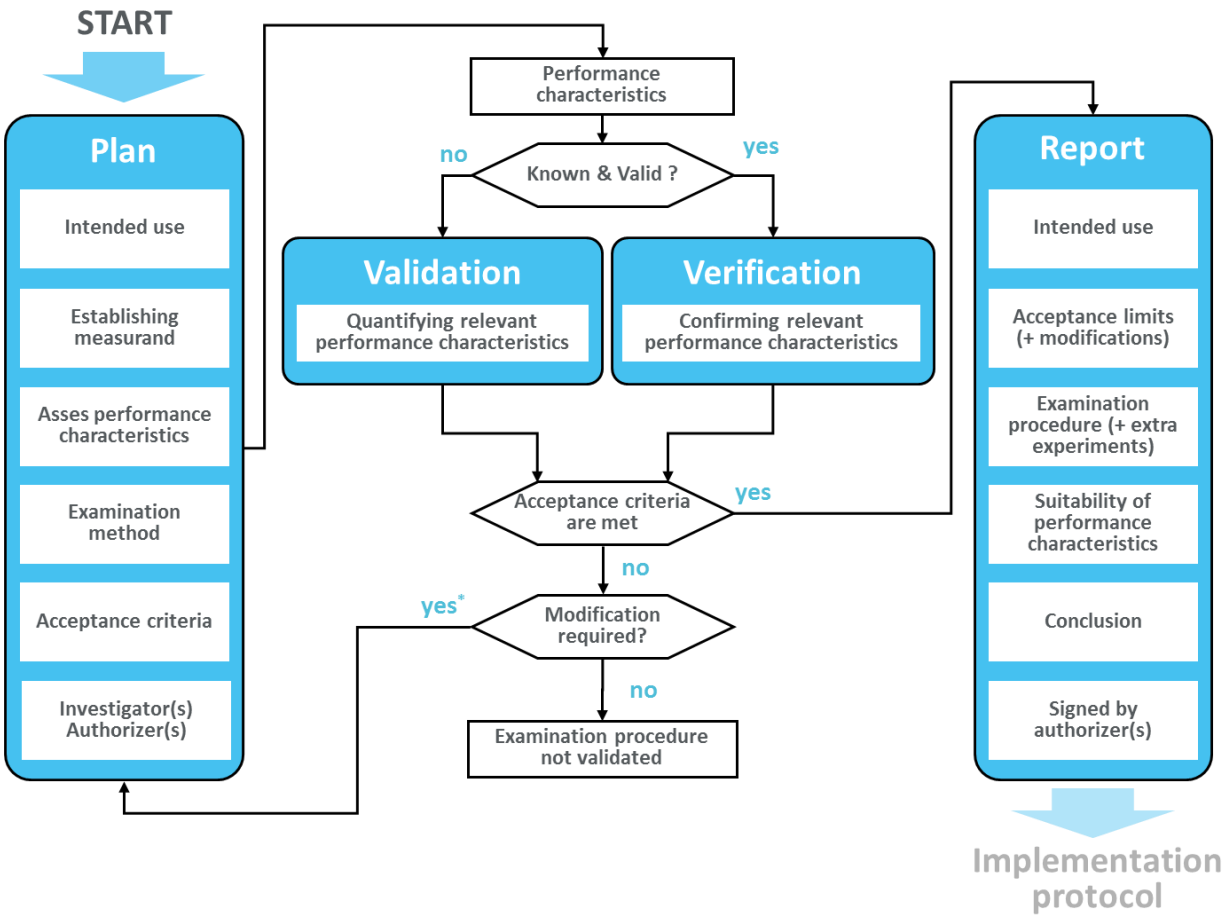

Figure 1. Schematic representation of the workflow for the validation and verification of examination procedures. According to ISO 15198, if a previously validated method is modified, the performance characteristics are per definition no longer valid and the relevant performance characteristics shall have to be validated. If the performance characteristics of

the modified examination procedures are already known and valid (for example, through validation by another laboratory) verification is sufficient.

7 Performance characteristics

The following possible relevant characteristics for validation are proposed in ISO 15189, section 5.5.1.3 (under NOTE): measurement trueness; measurement accuracy; measurement precision, including measurement repeatability and measurement intermediate precision; measurement uncertainty*; analytical specificity, including interfering substances; analytical sensitivity, detection limit and quantitation limit; measuring interval, diagnostic specificity and diagnostic sensitivity of the measurement. Whether or not these performance characteristics have to be examined is left to the judgement of the staff member with appropriate authority; in addition, examination should be statistically sound. Risk analysis may be an important element in the selection of the performance characteristics to be considered.

NOTE
* Measurement uncertainty contains bias and imprecision components. At the moment, measurement uncertainty is the subject of a separate ISO standard under development and therefore will not be discussed further here. See ISO 15189, section 5.5.1.4, NOTE 2.

X Recommendation

***In verification**, the staff member with appropriate authority shall take the following performance characteristics into consideration: measurement precision, measurement trueness, detection limits, stability, reference interval, medical decision values and interferences.*

XI Recommendation

***In validation**, the staff member with appropriate authority shall take into consideration all the performance characteristics named in section 7, accuracy excluded.*

XII Recommendation

Whenever specific performance characteristics are neither applicable nor feasible in view of the nature of the examination procedure or the prevalence of pathology, this should be documented and motivated.

The performance characteristics to be considered, including the terms necessary for their proper use, are briefly described below. Common models for establishing acceptance criteria for precision and bias can be found in the Milan consensus statement on this topic (see Background documents – section 4).

7.1 Measurement precision

Measurement precision refers, essentially, to repeatability and intermediate precision measured in the same laboratory. Reproducibility may also be of importance.

Repeatability (from measurement results)
Closeness of agreement among results of consecutive measurements of the same measurand in the same sample. This is performed under the same measuring conditions in a short time span, usually indicated as “within-run” precision.

Intermediate precision
Closeness of agreement between results of measurements of the same measurand, performed on the same sample under various measuring conditions (another series or day),

with the same or similar type of device or by the same analyst (where relevant). This is usually indicated as “between-run” precision.

Reproducibility
Closeness of agreement between results of measurement of the same measurand performed on the same or similar sample for measuring conditions at various locations and for various measuring systems.

Note: Reproducibility
Reproducibility is often defined as the ability to reproduce the same results in another laboratory using a specific examination procedure. However, in validation and verification we are, in fact, concerned with performance characteristics of an examination procedure in one’s own laboratory.

7.2 Measurement trueness

Measurement trueness (actual value) is sometimes confused with accuracy.
The metrological term “accuracy” contains both bias and imprecision, so use of the term “accuracy” for measurement trueness should be avoided.

Measurement trueness
Closeness of agreement between the average value, obtained from a large series of measurement results, and an accepted reference value (true value). The measure of trueness is usually expressed in terms of “bias”.

Bias
The difference between the average measurement results and the actual value or accepted reference value.

Reference material
Material or substance of which the property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials. If reference material is not available, the consensus value for external quality assessment may be used as reference value.

Traceability/metrological traceability
Traceability is a characteristic of a measurement result by which the result can be traced back to a reference material or SI-unit via an unbroken chain of calibrations.

Method comparison/method correlation
A statistical procedure based on data obtained from the paired analysis of the same samples using two different measuring procedures. This procedure is appropriate for comparing the laboratory method with a reference method by using a series of samples resembling patient material as closely as possible. The reference method is chosen to assess measurement trueness.
In practice a method comparison is also frequently used to compare a new method with the existing method and associated diagnostic decision limits.

7.3 Detection limits

Limit of Detection (LoD)
The lowest concentration/quantity of an analyte in a sample that can be detected with (stated) probability, although perhaps not quantified as an exact value.

Limit of Quantitation (LoQ)
Lowest amount of analyte in a sample that can be quantitatively determined with stated acceptable precision and trueness under stated experimental conditions

Measurement range
The range of the analyte values that an examination procedure can measure directly in the sample without dilution, concentration or other pre-treatment that is not part of the typical assay process.

7.4 Linearity

Linearity
The ability to provide results within a given measurement range that are directly proportional to the concentration (quantity) of an analyte in the test sample.

Increasing the measurement range
If the measurement range is extended in comparison with known performance characteristics by applying dilution or concentration, it will have to be validated separately.

Maximum dilution
The highest dilution at which the measurand can still be reliably measured.

7.5 Stability

Stability
The capacity of a measurand to not significantly change during a specific period and under conditions of storage and use anticipated in practice. Stability is not only of importance for the sample, but also for reagents, standards and controls.

7.6 Carry-over

Carry-over
Every form of influence of the measurand quantity exerted by one sample on another sample during the measurement process. Actually, this must also be considered for an interfering component that can be transmitted from one sample to another.

7.7 Analytical interferences

Interference
Clinically significant bias in the concentration of the measured analyte caused by another component or by properties of the sample.

Analytical specificity
The ability of a test or examination procedure to correctly identify or quantify an analyte in the presence of interfering substances/conditions. This characteristic is particularly dependent on the measurement principle used, but can vary depending on the class to which the chemical entity or matrix belongs. Analytical chemists use the term “selectivity” here.

Analytical sensitivity
The suitability of a method for detecting the intended analyte in the sample matrix. See also section 7.3.

Matrix effect

The influence of a property of the sample, rather than the analyte itself, on the measurement of the analyte using the relevant method, and therefore on the result.

7.8 Diagnostic characteristics

Reference interval

The biological reference interval is a defined interval for the distribution of values derived from the biological reference population. According to ISO 15189, the reference value is usually defined as the central interval comprising 95% of the measurement results of a healthy normal population.

A reference interval may depend on the type of primary sample, the pre-analytical phase and the analytical method followed. For example, glucose analysis for the fasting or non-fasting state; potassium analysis on serum vs. plasma, renin/aldosterone analysis for the supine or sitting state. Obsolete terms for reference interval are normal range or reference value(s).

Target value

The value pursued through an intervention due to it being linked to a specific health-related expectation.

Medical decision level

The value at which a medical intervention will take place or at which a clear conclusion can be drawn if this value is either exceeded or is not achieved.

Cut-off value

The point under or above which the measured value is considered to be deviant, i.e. clinically relevant.

Diagnostic sensitivity

The fraction or percentage of the patients **with** a specific clinical disorder for which the result of the relevant laboratory examination is positive. This can also be expressed as a percentage. In verification there is usually no question of a new relationship between the result of a test and a clinical condition. Thus, the trueness of the relationship does not have to be indicated, since this took place during the validation.

Diagnostic specificity

The fraction or percentage of the patients **without** a specific clinical disorder for which the result of the relevant laboratory examination is negative. This can also be expressed as a percentage. In verification there is usually no question of a new relationship between the result of a test and a clinical condition. Thus, the trueness of the relationship does not have to be indicated, since this took place during the validation.

8 Documentation

The documentation associated with a validation or verification consists of a validation/verification plan (see 6.2), the results, including the raw data and a validation/verification report, in which, besides the examination of the acceptance criteria, the implementation is also described.

XIII Recommendation

The results obtained shall be established and stored in a validation/verification report, at least for the period in which the examination procedure is in use.

XIV Recommendation

The results obtained shall be demonstrably evaluated using the acceptance criteria established in the validation/verification plan. The conclusion of the evaluation and whether or not it is appropriate for the intended use shall be established and archived in a validation/verification report. The validation/verification report shall be assessed and authorized by a staff member with the appropriate authority.

Note: the documentation is stored for the duration of use, extended with the (self-established) storage period of all other registrations pertaining to results from the laboratory.

9 Release, implementation and assurance

9.1 Release

A positive conclusion in the validation/verification report forms the basis for releasing the method for the intended use. The examination procedure to be released shall be described in a Standard Operating Procedure (SOP). An internal and external quality control system shall be established before the examination procedure may be released.

XV Recommendation

The release of an examination procedure on the basis of compliance with the acceptance criteria shall be carried out by a staff member with the appropriate authority, with a starting date stated in the documentation.

XVI Recommendation

The examination procedure investigated shall be documented in an SOP in compliance with ISO 15189.

XVII Recommendation

In implementing the method, an appropriate quality assurance procedure shall be established with acceptance limits for internal and external quality controls, taking into consideration decision limits of medical importance.

9.2 Implementation

Implementation of a new examination method requires communication to requesters and all the other parties on the relevant modifications arising from the results of the validation/verification. It will be necessary to establish an implementation procedure and/or checklist.

XVIII Recommendation

The process of implementation of a new or modified examination procedure shall be set out in an instruction or checklist.

The requester should be informed of modifications in reported results or examination procedures used that might have consequences for the interpretation by the requester.

XIX Recommendation

When modifications in examination procedures are judged to be of importance to the requester, how requesters are to be informed shall be documented.

9.3 Assurance

To provide assurance in the long term that the examination procedure functions in the same manner during the validation/verification, also after release, a procedure should be established for the use

and assessment of internal and external quality samples, including decision limits of medical importance.

XX Recommendation
There shall be a procedure by which it can be periodically ascertained if the original acceptance criteria for measurement precision and trueness, as determined during the validation/verification, are still met. If, upon reflection, more flexible criteria are justifiable, this should be substantiated.

References

See Normative references and Background documents (sections 3 and 4 of this document).

Annex 1

Notes on the Flowchart for various scenarios (Section 6.3 - Figure 1)

Validation process in the medical laboratory

1. Establishing the intended use of the examination procedure
2. Establishing the measurand
3. Consideration and selection of the performance characteristics
4. Establishing acceptance criteria for the intended use (shall take place without explicit previous knowledge of 6)
5. The manner in which the performance characteristics are established and examined against the acceptance criteria is established in a validation plan
6. Establishing the performance characteristics through objective evidence (the technical validation examination)
7. Establishing if performance characteristics meet the acceptance criteria, and specifying this in a validation report in which acceptance or rejection is concluded. If the results provide grounds for follow-up experiments not described in the validation plan, these experiments will be described in the validation report. If the performance characteristics do not meet the acceptance criteria as described in the validation plan, acceptance is only possible if the performance criteria do indeed meet the updated acceptance criteria. The validation report should in this case substantiate the update.

Verification process in the medical laboratory for an examination validated elsewhere

1. Establishing the intended use of the examination procedure
2. Establishing the measurand
3. Consideration and selection of the performance characteristics
4. Establishing acceptance criteria for the intended use
5. Selection of possible appropriate methods based on available documentation on performance characteristics
6. Establishing what performance characteristics shall, in view of the intended use, be examined in their own setting. All the performance characteristics are named in a verification plan; if, and how, one verifies that these performance characteristics meet the acceptance criteria is evaluated per characteristic.
7. Establishing a verification report through objective evidence, in which acceptance or rejection is concluded, and if relevant performance characteristics meet acceptance criteria. If the results provide grounds for follow-up experiments not described in the verification plan, they will be described in the verification report. If the performance characteristics do not meet the acceptance criteria as described in the verification plan, acceptance is then only possible if the performance criteria do indeed meet the updated acceptance criteria. The verification report should in this case substantiate the update.

Supplemental validation in a diagnostics laboratory desiring to use a previously **validated examination that has been modified**.

1. Establishing what performance characteristics, in view of the modification, may be relevantly different than established in a previous validation or verification.
2. Establishing a validation plan that describes how said performance characteristics will be established and what acceptance criteria they must meet.
3. Establishing if these performance characteristics meet acceptance criteria and specifying this in a validation report, in which acceptance or rejection is concluded. If the results provide grounds for follow-up experiments not described in the validation plan, they will be described in the validation report. If the performance characteristics do not meet the acceptance criteria as described in the validation plan, acceptance is only possible if the performance characteristics do indeed meet the updated acceptance criteria. The validation report shall in this case substantiate the update.

Verification on the basis of performance characteristics obtained **without intended validation (in compliance with ISO15189).**

1. Establishing the intended use
2. Establishing the measurand
3. Consideration and selection of the performance characteristics
4. Establishing acceptance criteria for the intended use
5. Evaluating to ascertain if previously established performance characteristics meet the acceptance criteria in which the previous study is used as validation
6. Establishing what performance characteristics shall, in view of the intended use, be examined in their own setting. All the performance characteristics are named in a verification plan, and are assessed per characteristic to ascertain if and how one verifies that these performance characteristics meet the acceptance criteria.
7. Establishing, through objective evidence, if relevant performance characteristics meet acceptance criteria in a verification report in which acceptance or rejection is concluded. If the results provide grounds for follow-up experiments not described in the verification plan, these shall be described in the verification report. If the performance characteristics do not meet the acceptance criteria as described in the verification plan, acceptance is only possible if the performance characteristics do indeed meet the updated acceptance criteria. The verification report should, in this case, substantiate the update.

<u>NOTE on updated acceptance criteria:</u>
If the method does not meet the acceptance criteria, acceptance can only be determined if the validation report does not document why this method was indeed not later examined against other (milder/updated) acceptance criteria, where attention continues to be paid to suitability of the intended use. Where the performance characteristics –also after revision – do not fall within the acceptance criteria, the validation report should explicitly reject acceptance.