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GUIDE

Fulfillment of Validation and Verification of Examination Requirements

Introduction

Purpose

This document from the Diagnostic Accreditation Program (DAP) provides guidance for organizations on fulfilling the Laboratory Medicine Accreditation Standards.

To meet user expectations and all other applicable accreditation and organizational requirements, laboratories must be able to produce validation and verification processes to all the equipment, instruments, analytical systems, examination methods, reagent kits, integral computer systems and functions, and documented procedures that will be in a new or changed process to verify that they are capable of achieving the required performance prior to implementation.

If you have questions about items in the standards, please email them to dap@cpsbc.ca.

Objectives

The objectives of this document are to

- familiarize medical laboratories with the concept of validation and verification of examination procedures,
- introduce the approaches laboratories can use to ensure methods and instruments are validated and verified, and
- describe the assessment of validation and verification of examination procedures.

Validation versus verification

What is validation of examination procedures?

Validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific, intended use are fulfilled. It is a process of evaluating method performance and demonstrating that it meets a particular requirement. Validation consists of a plan for laboratory personnel to challenge and record the results of any non-standard methods, laboratory-developed methods, and standard methods that are modified or used outside their intended scope. The validation process confirms that the examination procedure works as intended to meet user expectations and all applicable international,

national, and local accreditation and organizational requirements. All validations need to be documented, evaluated and approved by authorized and qualified personnel, and reviewed and approved by the laboratory's medical director or designate. A successful validation plan and record provide the necessary objective evidence or set of results from the validation studies to determine whether the laboratory's requirements for specific use or application have been met. It ensures that the method gives "correct" results and assures users of the correctness of the results.

Validations of examination methods are as extensive as is necessary to fully establish performance specifications. All results obtained, procedures used, acceptance criteria and a statement that the method is fit for intended use are all recorded or documented.

A validation plan may include the following types of studies to determine the method's performance specifications:

- imprecision studies (repeatability and reproducibility): within-run and between-run
- inaccuracy studies (trueness of measurement): patient comparison and interference studies
- analytical measurement range: linearity studies
- sensitivity/detection limit studies: lower limit of detection (LLOD) and lower limit of quantification (LLOQ)
- reference interval studies
- analysis of reference materials: National Institute of Standards and Technology (NIST) reference sample and/or proficiency testing material
- carryover studies
- recovery studies
- sample/reagent stability studies
- calibration stability studies
- measurement uncertainty studies

It is important to note that whenever changes are made, the revised examination procedure needs revalidation to ensure that it continues to meet the laboratory's expectations.

What is verification of examination procedures?

Whereas validation involves establishing performance specifications, verification is a means of demonstrating that a previously validated method by the manufacturer or other developers can meet the laboratory's defined analytical requirements, suitability and fit for use.

For unmodified commercial examination methods approved by Health Canada and accreditation organization or standard methods on condition that it is used within the scope of applicability, the laboratory needs to verify that it can perform the method and achieve results consistent with the stated claims for the method. The laboratory needs to demonstrate and verify that the performance specifications on new instruments and reagent kits or systems are comparable to those established by the manufacturer. The studies to perform these comparisons may comprise of the following:

- imprecision studies (repeatability and reproducibility): within-run and between-run
- inaccuracy studies (trueness of measurement): patient comparison and interference studies
- analytical measurement range: linearity studies
- sensitivity/detection limit studies: lower limit of detection (LLOD) and lower limit of quantification (LLOQ)
- reference interval studies: if the manufacturer's reference interval is not appropriate for the
- laboratory's patient population, the laboratory needs to establish its own ranges
- analysis of reference materials: National Institute of Standards and Technology (NIST) reference sample and/or proficiency testing material
- carryover studies
- recovery studies
- sample/reagent stability studies
- calibration stability studies

All verifications need documentation, acceptance criteria, evaluation and approval by authorized and qualified laboratory personnel and must be reviewed and approved by the laboratory's medical director or designate. Whenever changes are made, such as new reagent formulation, the revised examination procedure or method needs re-verification to ensure that the examination procedure or method continues to meet the laboratory's expectations.

Assessment of validation and verification

All of the criteria associated with the validation and verification of examination procedures are assessed at the regional or organizational level and at the facility. At the regional level, the assessor will review procedures to ensure that verification and validation plans have been developed. During the facility assessment, the assessor will confirm that the validation and verification plans have been implemented. The assessor will review records to ensure that the performance criteria have been met and the medical director or designate has approved and signed off on the validation and verification studies.

There are twenty-seven DAP criteria that directly address validation and verification of examination procedures:

EXA2.1.1	**M**	Equipment and measuring systems are approved by the national or provincial authority having jurisdiction over in vitro diagnostic measuring systems where applicable (e.g. Health Canada).
Evidence:		Specific records of approval of the equipment and measuring systems by the national or provincial authority having jurisdiction over in vitro diagnostic measuring systems where applicable (e.g. Health Canada).

Where:	Regional assessment
Comment:	Laboratories should have documentation that demonstrates the equipment and measuring systems are approved by Health Canada or other authorities that have jurisdiction over in vitro diagnostic measuring systems.

EXA2.1.2	**M**	The laboratory selects examination procedures which have been validated for their intended use. The identity of persons performing activities in examination processes is recorded. The specified requirements (performance specifications) for each examination procedure relate to the intended use of that examination. *Guidance: Preferred procedures include those specified by manufacturers for use in in vitro medical devices and those procedures that have been published in recommended textbooks, peer-reviewed literature or international consensus standards or guidelines, or national or regional regulations.*
Evidence:		Specific records of the specified requirements (performance specifications) for each examination procedure related to the intended use of that examination and the identity of the persons performing activities in examination processes.
Where:		Regional assessment
Comment:		Laboratories shall maintain documentation that details the specified requirements of each examination procedure.

EXA2.2.2	**M**	The laboratory obtains information from the manufacturer/method developer for confirming the performance characteristics of the procedure.
Evidence:		Specific records of the specified performance characteristics for each examination procedure as provided by the manufacturer/method developer.
Where:		Regional assessment
Comment:		Laboratories shall maintain documentation that details the performance characteristics established by the manufacturer/method developer to support the development of performance requirements.

EXA2.2.3	**M**	The independent verification by the laboratory confirms through obtaining objective evidence (in the form of performance characteristics) that the performance claims for the examination procedure have been met.
Evidence:		Specific records of the results of verification studies examination procedures, performed independently by the laboratory. Records shall include record of review of acceptability of performance.
Where:		Regional assessment
Comment:		Laboratories shall maintain documentation that details the independent verification studies performed on all examination procedures.

EXA2.2.4	**M**	The performance claims for the examination procedure confirmed during the verification process are those relevant to the intended use of the examination results.
Evidence:		Specific records of the performance specifications, that are relevant to the intended use of the examination results, established as part of the verification process.
Where:		Regional and facility assessment
Comment:		Laboratories must determine performance characteristics employed in verification studies to support determination of acceptability of examination procedures. Acceptability criteria must be established based on the intended use of the examination results.

EXA2.2.5	**M**	The laboratory documents the procedure used for the verification and record the results obtained. Staff with the appropriate authority review the verification results and record the review.
Evidence:		Specific records of the results of verification studies examination procedures, performed independently by the laboratory. Records shall include record of review of acceptability of performance by staff with the appropriate authority to review the results.
Where:		Regional and facility assessment
Comment:		Laboratories shall maintain documentation that details the verification studies performed on all examination procedures, including record of review. Where verification performance does not meet specified requirements review shall include documentation of considerations of acceptability of examination procedure.

EXA2.2.6	**M**	Verification uses the same material that will be used in the method.
Evidence:		Specific records of the material utilized in verification studies.
Where:		Regional assessment
Comment:		Laboratories must utilize material that will be used in the method throughout the verification process. The utilization of the same material throughout the verification process enables a clear understanding of examination performance as it would relate to patient care. Material that is not analogous to that which would be used in the method may not represent a true indicator of examination performance.

EXA2.2.7	When secondary verification occurs within a regional network the site performing secondary verification retains proof that performance expectations were achieved.
Evidence:	Specific procedures addressing the evaluation of new examination equipment which utilizes an examination method already verified within the regional network. The procedures should address all studies required to complete a secondary verification.
Where:	Regional assessment
Comment:	Verification of examination methods that have already been verified within a regional network need not complete as extensive of a verification prior to implementation. Utilization of secondary verification strategies allows for a gain in efficiency and a reduced scope of verification activities due to access to verification studies completed within the regional network.

EXA2.3.1	**M**	The laboratory validates examination procedures derived from non-standard methods; laboratory designed or developed methods, standard methods used outside their intended scope, and validated methods that are subsequently modified.
Evidence:		Specific records of the results of verification studies examination procedures including record of review of acceptability of performance.
Where:		Facility assessment
Comment:		A laboratory system must ensure new methods employed meet performance standards required to support safe patient care prior to implementation.

EXA2.3.2	**M**	Validation is as extensive as necessary and confirms through the provision of objective evidence that the specific requirements for the intended use of the examination have been fulfilled. *Guidance: Performance characteristics of an examination procedure should include consideration of 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.*
Evidence:		Specific records of the results of verification studies examination procedures including record of review of acceptability of performance.
Where:		Facility assessment
Comment:		A laboratory system must ensure new methods employed meet performance standards required to support safe patient care prior to implementation.

EXA2.3.3	**M**	Validation uses the same material that will be used in the method.
Evidence:		Specific records of the material utilized in validation studies.
Where:		Facility assessment
Comment:		Laboratories must utilize material that will be used in the method throughout the validation process. The utilization of the same material throughout the validation process enables a clear understanding of examination performance as it would relate to patient care. Material that is not analogous to that which would be used in the method may not represent a true indicator of examination performance.

EXA2.4.2	**M**	Results of validation or verification are recorded and compared to another valid examination (e.g. an existing examination method, sample exchange with a laboratory performing the same type of examination using similar methodology).
Evidence:		Specific records of the results of verification or validation studies which include a study that compares the examination procedure with another valid examination.
Where:		Facility assessment

Comment:	Laboratories should have documentation that examination procedures undergoing validation or verification compare with another valid examination.

EXA2.4.3	**M**	The laboratory documents the procedure used for the verification and records the results obtained. Staff with the appropriate authority reviews the verification results and records the review.
Evidence:		Specific records of the results of verification studies examination procedures, performed independently by the laboratory. Records shall include record of review of acceptability of performance by staff with the appropriate authority to review the results.
Where:		Regional and facility assessment
Comment:		Laboratories shall maintain documentation that details the verification studies performed on all examination procedures, including record of review. Where verification performance does not meet specified requirements review shall include documentation of considerations of acceptability of examination procedure.

EXA2.4.4	**M**	The medical director or designate determines the method acceptability based upon statistical analysis and medical outcome decisions.
Evidence:		Specific records of the results of verification studies which include record of review of acceptability of performance by the medical director or designate. Review shall include reference to statistical analysis and established performance characteristics.
Where:		Facility assessment
Comment:		Laboratories shall utilize statistical analysis to support objective determination of verification performance.

EXA2.4.5	**M**	Validation and verification, including approval by the medical director or designate, is completed prior to reporting patient results. Personnel involved in selection, verification and validation processes are recorded. Validation and verification documentation including approval is retained.
Evidence:		Specific records of the results of verification studies which include record of review of acceptability of performance by the medical director or designate.
Where:		Regional and facility assessment

Comment:	Laboratories shall maintain documentation that details the verification studies performed on all examination procedures, including record of review. Where verification performance does not meet specified requirements review shall include documentation of considerations of acceptability of examination procedure.

EXA2.5.1	**M**	When changes are made to a validated examination procedure, the influence of such changes is documented, and a new validation is performed.
Evidence:		Specific procedures addressing the evaluation of examination procedures when changes are made to a validated examination procedure.
Where:		Regional assessment
Comment:		Laboratories shall evaluate changes to validated examination procedures and document the influence those changes may have on assay performance. When changes are identified to impact examination performance verification studies are required to understand the extent of changes and appropriate action is taken.

EXA2.5.4	**M**	When an existing examination procedure is changed so that the results or interpretations could be significantly different, the implications are explained to users of the laboratory services after validating the procedure or when reporting results. *Guidance: This requirement can be accomplished in different ways, depending on local circumstances. Some methods include directed mailing, laboratory newsletters or part of the examination report itself.*
Evidence:		Specific records of user notification of differences in examination procedures performance.
Where:		Regional assessment
Comment:		Laboratories should have a process to notify users of any differences in examination procedures as a result of procedure changes.

Terms and definitions

accuracy	The closeness of agreement between a measured quantity value and the true quantity value of the measurand.	VIM[1]
analytical measurement range (AMR)	The range of analyte values that a method can directly measure of the specimen without any dilution, concentration, or other pretreatment not part of the usual assay process.	CLSI
comparability	Agreement between patient results obtained for a measurand using different measurement procedures within a healthcare system. Note: Results are considered to be comparable if the differences do not exceed a critical value established based on defined acceptance criteria.	CLSI
detection limit – lower limit of detection (LLOD)	Lowest amount of measurand in a sample that can be detected with (stated) probability, although perhaps not quantified as an exact value.	CLSI
detection limit – lower limit of quantitation (LLOQ)	Lowest amount of measurand in a sample that can be quantifiably determined with stated acceptable precision and trueness under stated experimental conditions.	CLSI
examination	A set of operations having the object of determining the value or characteristics of a property. Synonyms: analysis, assessment, investigation, measurement, study, test	ISO
imprecision	An expressed variation, either standard deviation or coefficient of variation, calculated from the results in a set of replicate measurements.	CLSI
linearity	Assuming no bias, the ability (within a given range) to provide results that are directly proportional to the concentration of the measurand in the test sample.	CLSI
measurand	Quantity intended to be measured. Synonym: analyte	CLSI
measurement uncertainty	A non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand based on the method used.	CLSI

procedure	A documented, specified way to carry out an activity of a process. Note: For the purposes of accreditation, procedures must always be documented, implemented and maintained.	ISO
process	A set of interrelated or interacting activities which transform inputs into outputs.	ISO
reference interval	A specified interval of the distribution of values taken from a biological reference population.	
sample	A discrete portion of a body fluid, breath, hair or tissue taken for examination of one or more quantities or properties assumed to apply for the whole. One or more parts taken from a primary sample. Synonyms: specimen, primary sample, aliquot	ISO
stability	Property of a measuring instrument, whereby its metrological properties remain constant in time.	CLSI
user (of laboratory services)	Physicians and others who order diagnostic examinations and/or receive diagnostic information and reports from laboratories. Synonyms: authorized requestor, ordering physician, clinical personnel	DAP
validation	Confirmation through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled. Note: The laboratory must validate non-standard methods, laboratory-designed or developed methods, standard methods used outside the intended scope, and validated methods that have been modified.	CLSI
verification	Confirmation through provision of objective evidence that specified requirements have been fulfilled. Note: The laboratory must verify validated examination procedures used without modification to confirm the performance characteristics of the procedure.	CLSI

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