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Guide to Fulfillment of Validation and Verification of Examination Requirements

Purpose

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

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

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

[1]International Organization for Standardization, International Vocabulary of Basic and General Terms in Metrology. Geneva: International Organization for Standardization; Geneva, Switzerland1993.

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

Introduction

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.

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.

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.

Assessing validation and verification of examination procedures

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.

DAP examination selection, validation and verification requirements

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

EXA2.1 There are procedures for the selection and evaluation 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).
EXA2.1.2	**M**	The laboratory selects examination procedures which have been validated for their intended use. *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.*
EXA2.1.3		There are procedures for the evaluation of new methods.
EXA2.2 There are processes for the verification of examination procedures.		
EXA2.2.1	**M**	The laboratory obtains information from the manufacturer for verifying the performance characteristics of the examination procedure.

EXA2.2.2	**M**	Validated examination procedures used without modification are independently verified prior to use.
EXA2.2.3	**M**	The independent verification by the laboratory confirms through obtaining objective evidence that performance characteristics have been met.
EXA2.2.4	**M**	Performance characteristics used in the verification process are relevant to the intended use of the examination.
EXA2.3 There are processes for the validation of examination procedures.		
EXA2.3.1	**M**	The laboratory validates examination procedures derived from non-standard methods such as, laboratory-designed or developed methods, standard methods used outside their intended scope, and validated methods that are subsequently modified.
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.
EXA2.3.3	**M**	Validation uses the same material that will be used in the method.
EXA2.4 The validation and verification of examination procedures is documented.		
EXA2.4.1	**M**	There are procedures for validation or verification of examination procedures.
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).
EXA2.4.3	**M**	Personnel with the required knowledge, expertise and authority review the results. The review is documented.
EXA2.4.4	**M**	The medical director or designate determines the method acceptability based upon statistical analysis and medical outcome decisions.

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.
Where required, validation and verification studies include documentation of:		
EXA2.4.6	**M**	• measurement accuracy
EXA2.4.7	**M**	• measurement precision at clinical decision levels
EXA2.4.8	**M**	• linearity to determine the measuring interval
EXA2.4.10	**M**	• correlation to review comparison and bias of the laboratory's patient data
EXA2.4.11	**M**	• sample stability to determine the maximum age of samples that can be tested
EXA2.4.12	**M**	• interference to determine constant and/or proportional interferences in the absence of manufacturer data
EXA2.4.13	**M**	• carry-over
EXA2.5 There are processes to address changes to examination procedures.		
EXA2.5.1	**M**	When changes are made to an examination procedure, the influence of such changes is documented, and a new validation is performed when required.
EXA2.5.2	**M**	The laboratory documents the procedure used for the validation of changes, and results are recorded.
EXA2.5.3	**M**	Authorized personnel review the validation results. This review is recorded.
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.

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