Establishment/Verification of Performance Specifications Policy

Purpose: This policy has been developed to meet the Clinical Laboratory Improvement Amendments (CLIA) Standard 493.1253 (Standard Requirements for Establishment and Verification of Performance Specifications).

Principle: Each laboratory that utilizes a Food and Drug Administration (FDA)-approved nonwaived test must verify that the performance specifications established by the manufacturer can be reproduced by the testing laboratory for the population of patients that the laboratory serves. Any laboratory that modifies an FDA-cleared or approved test, or introduces a test system not subject to FDA clearance or approval, or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patients test results, establish for each test system the performance specifications. In summary, CLIA Standard 493.1253 states that test systems used by the laboratory are subject to verification or establishment of performance specifications prior to reporting patient results.

The purpose of method validation or verification is to estimate how much error might be present in a test result produced by a method (or test system) in the laboratory. This information is used to ensure that the amount of error will not affect the interpretation of the test result and compromise patient care. If the observed errors are so large that they cause an incorrect result interpretation, then the method is not acceptable. To be acceptable, the errors need to be small relative to changes that will cause a change in the interpretation of a test result.

1. Definitions

1.1. Verification

1.1.1. Relates to confirmation that the laboratory using a test can replicate the manufacturer's performance claims when the test is used according to the package insert.

1.1.2. Verification applies to unmodified, nonwaived test systems that have been cleared or approved by the FDA.

1.2. Validation or establishment of performance
- 1.2.1. Relates to establishing the performance specifications for non-waived, laboratory-developed test systems at the time of assay development.
- 1.2.2. Establishing performance specifications is a one-time process that must be completed prior to reporting patient results.

1.3. Qualitative
- 1.3.1. Qualitative test systems provide non-numerical data.
- 1.3.2. The test system determines the presence or absence of the analyte in the specimen/sample; not quantity of the analyte.

1.4. Quantitative
- 1.4.1. Quantitative test systems provide numerical data.
- 1.4.2. The test system determines the quantity of the analyte present in the specimen/sample.

1.5. Accuracy (Trueness)
- 1.5.1. Accuracy is used to describe the extent to which a new test method is in agreement with a comparative or reference method.
- 1.5.2. Trueness must be evaluated in both quantitative and qualitative tests; verification and validation studies.

1.6. Precision
- 1.6.1. Precision is how well a given measurement can be reproduced when a test is applied repeatedly to multiple aliquots of a single homogeneous sample.
- 1.6.2. Precision is related entirely to random error caused by factors that vary during normal operation of the assay. Differences in the techniques of individual operators, pipettes, instruments may be a source of significant variation.
- 1.6.3. "Repeatability" and "reproducibility" are considered extreme measures of precision.
  - 1.6.3.1. Repeatability (or within run imprecision) is the smallest measurement of precision. The measurements are carried out under the same conditions (same operator, reagent lots, etc.)
  - 1.6.3.2. Reproducibility (or between run imprecision) is the largest measurement of precision. The measurements are carried out under changed conditions (different operator, reagent lots, etc.)

1.6.4. Precision must be evaluated in both quantitative and qualitative tests; verification and validation studies.

1.7. Analytical Sensitivity (Limit of Detection)
- 1.7.1. Analytical sensitivity is the ability of an assay to detect very low concentrations of a given substance in a biological specimen.
- 1.7.2. The limit of detection (LOD) is the lowest actual concentration of analyte in specimen that can be consistently detected (e.g., in ≥95% of specimens tested) with acceptable precision, but not necessarily quantified, under routine laboratory conditions and in a defined type of specimen.
- 1.7.3. LOD is expressed as a concentration such that the lower the detectable concentration of analyte, the greater the analytical sensitivity of the assay.
- 1.7.4. LOD must be evaluated in both quantitative and qualitative tests; validation studies only.

1.8. Analytical Specificity
- 1.8.1. Analytical specificity is the ability of a test system to detect only the intended target and that quantification of the target is not affected by cross-reactivity from related or potentially interfering substances.
- 1.8.2. The two aspects of analytical specificity are cross-reactivity and interference.
  - 1.8.2.1. Interfering substances refers to the effect that a compound other than the analyte in question has on the accuracy of measurement of an analyte.
  - 1.8.2.2. Cross-reactivity refers to the situation in which an analyte present in the sample, other than the target analyte, contributes to the reactivity observed.
- 1.8.3. Analytical specificity must be evaluated in both quantitative and qualitative tests; validation studies only.

1.9. Reportable Range (Linear Range)
- 1.9.1. Reportable or linear range is the span of test result values over which the laboratory can establish or verify the accuracy of the instrument or test system measurement response.
- 1.9.2. Only results that fall within the reportable range are reported.
- 1.9.3. The boundaries of the reportable range are the lowest and highest analyte concentrations that generate results that are reliably produced by a test method without dilution of the specimen. The lower limit must also be clinically relevant and acceptable for clinical use. The upper limit may be restricted by the highest available concentration in a sample or by the saturation of the signal generated by the instrument.

1.9.4. Reportable range must be evaluated in both quantitative and qualitative tests; verification and validation studies.

1.10. Reference Interval
- 1.10.1. This performance measure is not used to decide whether a method is acceptable or not.
- 1.10.2. Reference interval is the range of values typically found in individuals who do not have the disease or condition that is being assayed by the test (the "normal" population).
- 1.10.3. Reference intervals give clinicians practical information about what is "normal" and "abnormal" that can be used as a guide management of a patient.
- 1.10.4. Reference intervals must be evaluated in both quantitative and qualitative tests; verification and validation studies.

2. Test Systems Subject to Establishment or Verification of Performance Specifications

2.1. Test systems used by the laboratory are subject to establishment or verification of the performance specifications prior to reporting patient results. This applies to the following:
- 2.1.1. A test system that is introduced into the laboratory for the first time to measure an analyte that the laboratory has not previously measured;
- 2.1.2. A test system introduced for the first time into the laboratory for an analyte that the laboratory currently performs on an alternative test system;
- 2.1.3. An analyte added to a test system that can measure multiple analytes which the laboratory has been using for patient testing but has not previously reported patient results for this particular analyte; or
- 2.1.4. A modification to a test system that the laboratory has been using for patient testing should the modification affect performance specifications (ex. change in specimen handling, use of a different matrix, incubation times or temperatures, change in specimen or reagent dilution, using a different calibration material or changing the manufacturer set-points, and change or elimination of a procedural step).

2.2. When multiple instruments are used to perform the same test, performance specifications must be verified or established for each instrument.

2.3. Calibration and control procedures must be determined based upon the performance specifications verified or established.

2.3.1. Through the verification or establishment process, the frequency for calibration and control performance as well as the type, number, and concentration of materials used to monitor, detect error, and evaluate method performance must be determined.
2.3.2. The frequency for calibration and control performance must not be less than the frequency specified in the manufacturer's instructions.
2.3.3. The following must be considered when establishing the calibration and control frequency:
2.3.3.1. Test system instrument/reagent stability, including relocation;
2.3.3.2. Frequency with which the test is performed;
2.3.3.3. Technique dependence of the method;
2.3.3.4. Frequency of control failures; and
2.3.3.5. Training, experience and competency of the technical staff.

3. Unmodified, FDA-Cleared or Approved Test Systems

3.1. All unmodified, FDA-cleared or approved test systems must undergo a verification of performance specifications before reporting patient results.

3.2. The following performance specifications must be verified (e.g., demonstrate that the laboratory can obtain performance specifications comparable to those established by the manufacturer):
3.2.1. Accuracy;
3.2.2. Precision;
3.2.3. Reportable range of test results for the test system; and
3.2.4. Reference intervals (normal values) for the laboratory's patient population

3.3. If the performance specifications of the test system deviate from those claimed by the manufacturer, new performance specifications need to be established through a more comprehensive validation process. See Section 4.

4. Modified, FDA-Cleared or Approved Test Systems, Introduced Test Systems not Subject to FDA Clearance or Approval (In-House Developed), and Test Systems in which Performance Specifications are not provided by the Manufacturer

4.1. All modified, FDA-cleared or approved test systems, in-house developed, and test systems in which performance specifications are not provided by the manufacturer must undergo establishment of performance specifications before reporting patient results.

4.1.1. These test systems are considered laboratory-developed or homebrew test systems.

4.2. The following performance specifications must be established, as applicable:
- 4.2.1. Accuracy;
- 4.2.2. Precision;
- 4.2.3. Analytical sensitivity;
- 4.2.4. Analytical specificity;
- 4.2.5. Reportable range of test results (upper and lower limits of the test system); and
- 4.2.6. Reference intervals (normal values) for the laboratory's patient population

4.3. Laboratory test report disclaimers:
- 4.3.1. For ODHL-validated laboratory-developed diagnostic assays: The performance characteristics of "insert assay name" were determined by the Ohio Department of Health Laboratory. It has not been cleared or approved by the FDA.
- 4.3.2. For ODHL epidemiologic assays: "Insert assay name" was performed for epidemiological purposes only; it has not been cleared or approved by the FDA. The test results must not be used for assessment, diagnosis or treatment of patients.
- 4.3.3. For research use only (non-validated assays): "Insert assay name" has not been cleared or approved by the FDA for "insert information". The assay has not been validated by ODHL for use on "insert information"; test results were obtained with research procedures. Test results must not be used for assessment, diagnosis, or treatment of patients.

5. Development/Submission of Verification or Validation Plans

5.1. Before a test system undergoes verification or validation testing, a verification or validation plan must be developed. The plan will include the following sections:
- 5.1.1. Purpose of the study
- 5.1.2. Study design:
  - 5.1.2.1. Method used as comparison (as applicable);
  - 5.1.2.2. Definitions of true positive, true negative, false positive and false negative (as applicable);
  - 5.1.2.3. Detailed information on the types and numbers of specimens to be tested to address each of the required verification or validation performance characteristic (See sections 3 and 4 above); and

5.1.2.4. Procedure for resolving discrepant results or for addressing additional means to meet criteria, such as increasing the sample size should this be necessary.

5.1.3. Acceptance criteria for each performance characteristic being evaluated.

5.1.4. Approval signatures (developer of plan, supervisor and laboratory director).

5.2. The plan will be submitted to the Laboratory Director for approval prior to implementation of the plan.

6. Completion of Verification or Validation Studies

6.1. A verification or validation summary sheet will be completed for each study. The summary sheet will include calculated performance data, recommendation for either accepting or not accepting the new or modified test, and appropriate signatures.

6.2. Prior to a test being put into practice and prior to any results being reported, the study must be approved by the Laboratory Director and the following items must be developed and reviewed/approved by the Laboratory Director.

6.2.1. A standard operating procedure;

6.2.2. Training documentation, including documentation for the person performing the study;

6.2.3. Reports or calculations produced by a laboratory information system (LIS);

6.2.4. Assay turnaround time;

6.2.5. Enrollment or participation in a proficiency test program;

6.2.6. Cost per test analysis; and

6.2.7. A contingency plan that establishes an alternative or send-out laboratory is to be created and included in the procedure manual.

7. Record Retention

7.1. The verification or validation summary sheet and all data will be kept in the laboratory where the test is performed. It is acceptable to keep the documents in an electronic format.

7.2. The documentation will be kept for the duration of the test being used at the laboratory.

8. References

8.1. Burd, E. M. 2010. Validation of Laboratory-Developed Molecular Assays for Infectious Diseases. Clin. Microbiol. Rev. **23**:550-576.

8.2. Clinical and Laboratory Standards Institute (CLSI). Establishing Molecular Testing in Clinical Laboratory Environments; Approved Guideline. CLSI document MM19-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.
8.3. Westgard, J. O. 2003. Basic Method Validation. Westgard QC, Inc., Madison, WI.
8.4. Cumitech 31A. Verification and Validation of Procedures in the Clinical Microbiology Laboratory, American Society for Microbiology Press, 2009.

Signature Approvals

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QA Officer Date

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Laboratory Director Date