COLLEGE of AMERICAN PATHOLOGISTS

Master

All Common Checklist

CAP Accreditation Program

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TEST METHOD VALIDATION AND VERIFICATION - NONWAIVED TESTS

NOTE: This section does not apply to waived tests performed following manufacturer's instructions.

ANALYTICAL VALIDATION/VERIFICATION

Analytical verification is the process by which a laboratory determines that an unmodified FDA-cleared/approved test performs according to the specifications set forth by the manufacturer when used as directed. Analytical validation is the process used to confirm with objective evidence that a laboratory-developed or modified FDA-cleared/approved test method or instrument system delivers reliable results for the intended application. See below for requirements for laboratories not subject to US regulations.

Laboratories are required to perform analytical validation or verification of each nonwaived test, method, or instrument system before use in patient testing, regardless of when it was first introduced by the laboratory, including instruments of the same make and model and temporary replacement (loaner) instruments. ***There is no exception for analytical validation or verification of tests introduced prior to a specific date.*** *The laboratory must have data for the validation or verification of the applicable method performance specifications and retain the records as long as the method is in use and for at least two years after discontinuation.*

If an FDA-cleared or approved method was verified by someone other than the laboratory's personnel (eg, manufacturer's representative), the laboratory must ensure that the verification correlates with its in-house test performance by showing confirmation of performance specifications by laboratory personnel testing known specimens.

The method performance specifications (ie, the applicable analytic performance characteristics of the test, such as accuracy, precision, etc.) must be validated or verified in the location in which patient testing will be performed. If an instrument is moved, the laboratory is responsible for determining that the method performance specifications are not affected by the relocation process or any changes due to the new environment (eg, refer to the manufacturer's manual regarding critical requirements, such as set-up limitations, environmental conditions, etc.). The laboratory must follow manufacturer's instructions for instrument set up, maintenance, and system verification. Separate requirements for verifying the performance of instruments and equipment to confirm that they function according to expectations for the intended use and within the defined tolerance limits are found in the Instrument and Equipment Maintenance and Function Checks section (COM.30550, COM.30600).

QUALITATIVE TESTING

Not all method performance specifications apply to qualitative tests. For qualitative tests, the laboratory must verify or establish the method performance specifications that are applicable and clinically relevant.

LABORATORIES SUBJECT TO US REGULATIONS:

- *For unmodified FDA-cleared or approved tests, the laboratory may use information from manufacturers, or published literature, but the laboratory must verify such outside information on accuracy, precision, reportable range, and reference intervals.*
- *For modified FDA-cleared or approved tests and laboratory-developed tests (LDTs), the laboratory must establish accuracy, precision, analytical sensitivity, analytical specificity (interferences), reportable range, and reference intervals, as applicable; data on interferences may be obtained from manufacturers or published literature, as applicable.*

LABORATORIES NOT SUBJECT TO US REGULATIONS:

- *For laboratories performing tests approved by an internationally recognized regulatory authority (eg, the European Union's Conformité Européenne (CE) Marking), the laboratory may use information from manufacturers, or published literature, but the laboratory must verify such outside information on accuracy, precision, reportable range, and reference intervals. Analytical verification must also follow national, federal, state (or provincial), and local laws and regulations for approval and usage of such tests. These instruments and devices are not considered laboratory-developed tests in laboratories not subject to US regulations.*
- *For tests not approved by an internationally recognized regulatory authority, the laboratory must perform analytic validation to establish accuracy, precision, analytic sensitivity, analytical specificity (interferences), reportable range, and reference intervals, as applicable; data on interferences may be obtained from manufacturers or published literature, as applicable.*

LABORATORY-DEVELOPED TESTS:
For the purposes of interpreting the checklist requirements, a laboratory-developed test (LDT) is defined as follows: A test used in patient management that has both of the following features:

1. *The test is performed by the clinical laboratory in which the test was developed wholly or in part;* ***AND***
2. *The test is neither FDA-cleared nor FDA-approved (or, for laboratories not subject to US regulations, the test is not approved by an internationally recognized regulatory authority).*

EMERGENCY USE AUTHORIZATION (EUA)
For laboratories subject to US regulations, an emergency use authorization (EUA) is the legal mechanism used by the FDA to allow the use of an unapproved medical product (eg, diagnostic device) or an unapproved use of an approved medical product during an emergency to diagnose, treat, or prevent a serious or life threatening disease condition caused by a chemical, biological, radiological, or nuclear agent (CBRN).

A laboratory that uses an EUA assay may not be able to establish accuracy, precision, analytical sensitivity, analytical specificity (interferences), reportable range, and reference interval studies. Laboratories using an EUA assay must follow the assay or test system's protocol as authorized by the FDA without modification and document the alternative mechanism employed to ensure accurate test results.

Information on current EUA assays can be found on the FDA website at the following link;
https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm

Inspector Instructions:

	• Policies and procedures for the introduction of new tests, methods, or instruments • Sampling of assay validation and verification studies with emphasis on tests introduced in the past two years, especially high volume tests and tests with the highest risk to patients • Sampling of patient reports for laboratory-developed assays
	• Which laboratory tests or instruments have been implemented in the past two years, particularly those that are not FDA-cleared/approved? • Do you follow the manufacturer's instructions exactly for all FDA-cleared/approved diagnostic kits or devices? • For laboratories not subject to US regulations, do you follow the manufacturer's instructions exactly for tests approved by an internationally recognized regulatory authority? • How does your laboratory validate or verify assay performance prior to test implementation? • How does your laboratory verify or establish reference intervals? • How does your laboratory validate clinical claims made by the laboratory about LDTs?
	• Select at least one validation or verification study performed for each type of instrument or method introduced during the past two years.

DISCOVER

- In addition, select assays for evaluation if recurrent problems have been identified in proficiency testing results, quality control, competency assessment, or physician complaints regardless of how long the assay has been in place.
- Review validation or verification records to confirm that appropriate studies were performed using an adequate number of cases, and a written assessment of the data was performed. If the data showed discordances or unacceptable variations, investigate how they were resolved. If a study was not performed or is missing required components, cite the appropriate related requirement(s) (eg, COM.40300, COM.40325, COM.40350).
- Confirm that the written assessment of each component (accuracy, precision, interferences, etc.) of the validation or verification studies has been approved by the laboratory director (or qualified designee) prior to the initiation of clinical testing. If the study assessment was not signed by the laboratory director or designee, cite COM.40475.
- Review examples of patient reports for laboratory-developed tests and modified FDA-cleared/approved tests to identify clinical claims being made by the laboratory for the testing. Confirm that studies were performed.

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COM.40250 Manufacturer's Instructions **Phase II**

The laboratory follows manufacturer's instructions or provides validation records if the test has been modified.

NOTE: Following manufacturer's instructions includes performing quality control, calibration, calibration verification, and related functions as applicable to the scope of testing. Reagents, fluids, and disposable materials supplied by the laboratory must meet the specifications in the instructions.

If the laboratory modifies manufacturer's instructions, the test is no longer FDA-cleared/approved, and the modification(s) must be validated by the laboratory. This requirement also applies to laboratories not subject to US regulations for tests approved by an internationally recognized regulatory authority that are modified by the laboratory. Changes in the specimen type or collection device are examples of common modifications (see "modification of manufacturer's instructions" in the Definition of Terms). Additional requirements for validation/verification may be found in the discipline-specific checklists.

For waived and moderately complex tests, if manufacturer instructions are modified, requirements for high complexity testing apply.

Evidence of Compliance:

✓ Validation records of established performance specifications (accuracy, precision, analytical sensitivity, analytical specificity, interferences, reference interval(s), and reportable range) of any test that has been modified.

REFERENCES
1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register.* 2003(Jan 24): [42CFR493.1252]

***REVISED** *06/04/2020*

COM.40300 Verification of Test Performance Specifications - FDA-cleared/approved Tests **Phase II**

Prior to clinical use of each unmodified FDA-cleared or approved test, the laboratory has performed a verification study and prepared a written assessment of each of the following test method performance specifications, as applicable, using a sufficient number of characterized samples:

1. **Analytical accuracy**
2. **Analytical precision**
3. **Reportable range**

NOTE 1: Accuracy is verified by comparing results to a definitive or reference method, or an established comparative method. Use of matrix-appropriate reference materials, patient specimens (altered or unaltered), or other commutable materials with known concentrations or activities may be used to verify accuracy. The use of routine quality control materials or calibrators used to calibrate the method is not appropriate.

NOTE 2: Precision is verified by repeat measurement of samples at varying concentrations/activities within run and between run over a period of time.

NOTE 3: The reportable range of an assay is the range of values that the laboratory reports for that assay.

NOTE 4: If multiple identical instruments or devices are in use, there must be records (data and written assessment) showing that the method performance specifications have been separately verified for each test and instrument or device.

NOTE 5: If a method is verified by someone other than the laboratory's personnel (eg, manufacturer's representative), the laboratory must have records to show that the verification correlates with its in-house test performance by showing confirmation of performance specifications by the laboratory personnel testing known specimens.

NOTE 6: The requirement for a written assessment applies to all tests implemented after June 15, 2009; however, all nonwaived tests must have records of completed analytical verification, regardless of the implementation date. The written assessment must include an evaluation of each component of the verification study, including the acceptability of the data. If data include discordant results, there must be a record of the discordance and investigation of any impact on the approval of the test for clinical use.

Evidence of Compliance:

- ✓ Written procedure for verifying test method performance specifications **AND**
- ✓ Records of verification and written assessment of each component of the test method performance specifications for each test

REFERENCES

1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register.* 2003(Jan 24) [42CFR493.1253]
2) Clinical and Laboratory Standards Institute. *Preliminary Evaluation of Quantitative Clinical Laboratory Methods; Approved Guideline.* 3rd ed. CLSI document EP10-A3-AMD. Clinical and Laboratory Standards Institute, Wayne, PA; 2014.
3) Clinical and Laboratory Standards Institute. *A Framework for Using CLSI documents to Evaluate Clinical Laboratory Measurement Procedures. 2nd ed.* CLSI report EP19-ED2. Clinical and Laboratory Standards Institute, Wayne, PA; 2015.
4) Clinical and Laboratory Standards Institute. *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline. 3rd ed.* CLSI document EP05-A3. Clinical and Laboratory Standards Institute, Wayne, PA; 2014.
5) Clinical and Laboratory Standards Institute. *Evaluation of the Commutability of Processed Samples; Approved Guideline. 3rd ed.* CLSI document EP14-A3. Clinical and Laboratory Standards Institute, Wayne, PA; 2014.

***NEW** 06/04/2020*

COM.40325 Verification of Test Performance Specifications - Tests Approved by an Internationally Recognized Regulatory Authority - Laboratories not Subject to US Regulations **Phase II**

For laboratories not subject to US regulations, prior to clinical use of each test approved by an internationally recognized regulatory authority (eg, the European Union's Conformité Européenne (CE) Marking), the laboratory has performed a verification study and prepared a written assessment of each of the following test method performance specifications, as applicable, using a sufficient number of characterized samples:

1. **Analytical accuracy**

2. **Analytical precision**
3. **Reportable range**
4. **Any other performance characteristic required to ensure analytical test performance**

NOTE 1: Accuracy is verified by comparing results to a definitive or reference method, or an established comparative method. Use of matrix-appropriate reference materials, patient specimens (altered or unaltered), or other commutable materials with known concentrations or activities may be used to verify accuracy. The use of routine quality control materials or calibrators used to calibrate the method is not appropriate.

NOTE 2: Precision is verified by repeat measurement of samples at varying concentrations or activities within run and between run over a period of time.

NOTE 3: The reportable range of an assay is the range of values that the laboratory reports for this assay.

NOTE 4: The laboratory must also validate analytic sensitivity (lower detection limit) and analytic specificity (interferences) if the test manufacturer has not documented these test characteristics. Data on interferences may be obtained from manufacturers or published literature, as applicable. The laboratory must validate other relevant analytic characteristics not documented by the test manufacturer, as appropriate.

NOTE 5: If multiple identical instruments or devices are in use, there must be records (data and written assessment) showing that the method performance specifications have been separately verified for each test and instrument or device.

NOTE 6: If a method is verified by someone other than the laboratory's personnel (eg, manufacturer's representative), the laboratory must have records to show that the verification correlates with in-house test performance by showing confirmation of performance specifications by the laboratory personnel testing known specimens.

NOTE 7: The requirement for a written assessment applies to all tests implemented after June 15, 2009; however, all nonwaived tests must have records of completed analytical verification, regardless of the implementation date. The written assessment must include an evaluation of each component of the verification study, including the acceptability of the data; If data include discordant results, there must be a record of the discordance and investigation of any impact on the approval of the test for clinical use.

Evidence of Compliance:

✓ Written procedure for verifying test method performance specifications **AND**
✓ Records of the test method performance specifications for each test

REFERENCES
1) Clinical and Laboratory Standards Institute. *Preliminary Evaluation of Quantitative Clinical Laboratory Methods; Approved Guideline.* 3rd ed. CLSI document EP10-A3-AMD. Clinical and Laboratory Standards Institute. Wayne, PA; 2014.
2) Clinical and Laboratory Standards Institute. *A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures.* 2nd ed. CLSI report EP19-ED2. Clinical and Laboratory Standards Institute. Wayne, PA; 2015.
3) Clinical and Laboratory Standards Institute. *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline.* 3rd ed. CLSI document EP05-A3. Clinical and Laboratory Standards Institute. Wayne, PA; 2014.
4) Clinical and Laboratory Standards Institute. *Evaluation of the Commutability of Processed Samples; Approved Guideline.* 3rd ed. CLSI document EP14-A3. Clinical and Laboratory Standards Institute. Wayne, PA; 2014.

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COM.40350 Validation of Test Performance Specifications - Modified FDA-cleared/approved Tests and LDTs **Phase II**

Prior to clinical use of each modified FDA-cleared or approved test and laboratory-developed tests (LDTs), the laboratory has performed a validation study and prepared a written assessment of each of the following test method performance specifications, as applicable, using a sufficient number of characterized samples:

1. **Analytical accuracy**
2. **Analytical precision**
3. **Reportable range**
4. **Analytical sensitivity (lower detection limit)**
5. **Analytical specificity**
6. **Any other performance characteristic required to ensure analytical test performance**

NOTE 1: For laboratories not subject to US regulations, this requirement also applies to:

- *Tests that are not approved by an internationally recognized regulatory authority*
- *Approved tests that have been modified by the laboratory*

NOTE 2: Accuracy is validated by comparing results to a definitive or reference method, or an established comparative method. Use of matrix-appropriate reference materials, patient specimens (altered or unaltered), or other commutable materials with known concentrations or activities may be used to validate accuracy. The use of routine quality control materials or calibrators used to calibrate the method is not appropriate.

For laboratory-developed tests, an appropriate number of samples to demonstrate analytical accuracy is defined as the following:

- *For quantitative tests, a minimum of 20 samples with analyte concentrations distributed across the analytical measurement range should be used. Proportionate mixtures of samples may be used to supplement the study population.*
- *For qualitative tests, a minimum of 20 samples, including positive, negative, and low-positive samples with concentrations near the lower level of detection should be used; equivocal samples should not be used.*
- *For certain methods that test multiple analytes (g, next-generation sequencing, FISH, HPLC, GC-MS, MALDI-TOF, etc.), analytic accuracy may be established for each method (not necessarily each analyte), as appropriate.*

If the laboratory uses fewer samples, the laboratory director must record the criteria used to determine the appropriateness of the sample size. In many cases, a validation study with more samples is desirable.

For LDTs in use prior to July 31, 2016, for which limited validation studies are recorded, ongoing data supporting acceptable test performance may be used to meet the above minimum sample requirement, unless the laboratory director has recorded the criteria used to determine the acceptability of a smaller sample size. Examples of such ongoing data include records of proficiency testing, alternative performance assessment, quality control, and correlation with clinical data.

NOTE 3: Precision is validated by repeat measurement of samples at varying concentrations or activities within-run and between-run over a period of time.

NOTE 4: The reportable range of an assay is the range of values that the laboratory reports for that assay.

NOTE 5: Examples of other performance characteristics required for analytical test performance include specimen stability, reagent stability, linearity, carryover, and cross-contamination, as appropriate and applicable.

NOTE 6: If multiple identical instruments or devices are in use, there must be records (data and written assessment) showing that the method performance specifications have been separately validated for each test and instrument or device.

NOTE 7: The requirement for a written assessment applies to all tests implemented after June 15, 2009; however, all nonwaived tests must have records of completed analytical validation, regardless of the implementation date. The written assessment must include an evaluation of each component of the validation study, including the acceptability of the data. If data include discordant results, there must be a record of the discordance and investigation of any impact on

the approval of the test for clinical use.

NOTE 8: This checklist requirement does not apply to LDTs that employ the following methods:

- *Manual microscopy (eg, histopathologic and cytologic interpretation, microscopic examination of blood or body fluids, Gram stains)*
- *Conventional microbiologic cultures and disc/broth/tube susceptibility studies*

Evidence of Compliance:

- ✓ Written procedure for validating test method performance specifications **AND**
- ✓ Records of validation and written assessment of each component of the test method performance specifications

REFERENCES

1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register.* 2003(Jan 24) [42CFR493.1253]
2) Clinical and Laboratory Standards Institute (CLSI). *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline.* 4th ed. CLSI document C24-ED4. Clinical and Laboratory Standards Institute, Wayne, PA, 2016.
3) Clinical and Laboratory Standards Institute. *A Framework for Using CLSI documents to Evaluate Clinical Laboratory Measurement Procedures. 2nd ed.* CLSI report EP19-ED2. Clinical and Laboratory Standards Institute, Wayne, PA; 2015.
4) Clinical and Laboratory Standards Institute (CLSI). *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline. 2nd ed.* CLSI document EP17-A2. Clinical and Laboratory Standards Institute, Wayne, PA; 2012.
5) Clinical and Laboratory Standards Institute. *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline.* 3rd ed. CLSI document EP05-A3. Clinical and Laboratory Standards Institute, Wayne, PA; 2014.
6) Clinical and Laboratory Standards Institute. *Evaluation of the Commutability of Processed Samples; Approved Guideline.* 3rd ed. CLSI document EP14-A3. Clinical and Laboratory Standards Institute, Wayne, PA; 2014.

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COM.40475 Method Validation and Verification Approval - Nonwaived Tests **Phase II**

Prior to clinical use of each nonwaived test, the laboratory director, or designee meeting CAP director qualifications, has signed the laboratory's written assessment of the validation or verification study (accuracy, precision, etc.) to confirm the acceptance of the study data and written assessment, and to approve each nonwaived test for clinical use.

NOTE: This checklist requirement is applicable only to nonwaived tests implemented after June 15, 2009; however, all nonwaived tests must have records of completed analytical validation or verification, regardless of their implementation date.

The approval must include: 1) review of the written assessment of the validation or verification study, including the acceptability of the data and investigation of any discordant results; 2) signed approval statement, such as, "I have reviewed the verification (or validation) data for the performance specifications listed below for the (insert instrument/test name), and the performance of the method is considered acceptable for patient testing."

If a validation or verification study (accuracy, precision, reportable range, etc.) was not performed or is missing required components, the appropriate, related checklist requirements must also be cited (eg, COM.40300, COM.40350).

If multiple identical instruments or devices are in use, there must be records (data and written assessment) showing that the method performance specifications have been separately validated/verified for each test and instrument or device.

Evidence of Compliance:

- ✓ Records of approval of validation and verification studies and approval for clinical use

REFERENCES

1) Lawrence Jennings, Vivianna M. Van Deerlin, Margaret L. Gulley (2009) Recommended Principles and Practices for Validating Clinical Molecular Pathology Tests. *Archives of Pathology & Laboratory Medicine*: Vol. 133, No. 5, pp. 743-755
2) Lacbawan FL, Weck KE, Kant JA, Feldman GL, Schrijver; Biological and Molecular Genetic Resource Committee of the College of American Pathologists. Verification of performance specifications of a molecular test: cystic fibrosis carrier testing using the Luminex liquid bead array. *Arch Pathol Lab Med.* 2012. Jan; 136(1):14-9.
3) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register.* 2003(Jan 24) [42CFR493.1253]