FDA Approved Unmodified Tests

The majority of laboratories will perform FDA approved unmodified tests. The laboratory is required to verify the manufacturer's stated performance specifications for each FDA-approved unmodified test system introduced.

Prior to patient testing, each of the following performance specifications must be verified and documented for each non-waived test or method:

Accuracy: The ability of the test system to obtain the real value of the substance tested

Precision: The ability of the test system to obtain the same result upon repetitive testing

Reference range: The range of values expected for a given population (normal range)

Reportable range: The range, from the lowest to highest value, for which the laboratory can verify the accuracy of the test system. The reportable range cannot exceed the highest or lowest value of the known standard used to verify the test system. Patient results which exceed this range (either high or low) must be reported as greater than or less than the maximum or minimum standard value, or be diluted.

Non-FDA Approved tests (includes modified FDA approved tests)

The laboratory is required to establish performance specifications for each FDA approved but modified, non-FDA approved, or in-house developed test system prior to conducting patient testing. Each instrument's performance must be established – even if there are multiple instruments of the same make and model.

Prior to patient testing, the performance specifications for each FDA approved but modified, non-FDA approved, or in-house developed test system, must be established and documented for:

- Accuracy
- Precision
- Reportable range
- Reference range
- Analytical sensitivity
- Analytical specificity (including evaluation of interfering substances)
- Specimen stability
- Any other performance characteristics required for accurate test performance

Modifications of FDA Approved Systems

The following items are defined as modifications of FDA approved test systems by CMS:

- Change in specimen handling instructions
- Change in incubation times or temperatures
- Change in specimen or reagent dilution
- Using a different antibody (source, monoclonal-vs.-polyclonal)
- Change or elimination of a procedural step
- Change or addition of detector (conjugate) or substrate
- Change in the solid phase
- Change in the cutoff or method of calculating the cutoff for semi-quantitative assays
- Change in the endpoint or calculation of the endpoint
- Addition of adsorbent
- Change in the strain or antigen in serologic assays
- Changing the calibrator/reference material

VERIFICATION OF PERFORMANCE SPECIFICATIONS

Introduction:

There are 2 paths for determination of performance specifications. The lab will need to determine the applicable path based on whether the test method is FDA Approved or non-FDA Approved. For assistance call or email COLA.

A) Unmodified, FDA approved Test Systems:

The laboratory is required to verify performance specifications for each unmodified, FDA approved test system introduced after 4/24/2003. (VER 1-4 and VER 12).

Verification ensures that the test system is operating according to expected performance standards and is capable of producing accurate and reliable results. Key points to verification of performance specifications:

- The process for verification of performance specifications should be established by the Lab Director in consultation with the Clinical Consultant/Technical Supervisor and the manufacturer.
- Must be performed in your laboratory by your staff.
- Data must be reviewed and evaluated to determine acceptability by the LD, prior to initiating patient testing.
- Laboratory must document all data collection and validation and retain for as long as method is in use plus 2 years.
- Introduction of loaner instruments and relocation of existing instrument, require verification/re-verification of acceptable performance specifications.
- Each instrument's performance must be verified – even if there are multiple instruments of the same make and model.

Prior to patient testing, have each of the following performance specifications been verified and documented for each non-waived test or method: (VER 1-4)

VER 1 R

Accuracy?

When the real value of the substance tested is obtained.

VER 2 R

Precision?

When the same number is obtained upon repetitive testing.

VER 3 R

Reportable patient range?

The range is from the lowest to highest value for which the laboratory can verify the accuracy of the test system. The reportable range for patient results cannot exceed the highest or lowest value of the known standard used to verify the test system. Patient results which exceed this range (either high or low) must be reported as greater than or less than the maximum or minimum standard value unless another procedure has been developed to adjust for specimens beyond the maximum range.

VER 4R

Reference range?

The range of values expected for a given population.

B) FDA Approved Methods Modified by the Lab, Non-FDA Approved Methods, and Test Methods Developed by the Laboratory In-House.

The laboratory is required to establish performance specifications for each FDA-approved but modified, non FDA approved, or in house developed test system prior to conducting patient testing. (VER 5-11). Each instrument's performance must be verified – even if there are multiple instruments of the same make and model.

This ensures that the test system is operating according to expected performance standards and is capable of producing accurate and reliable results. The following are examples of modifications of FDA approved test systems. This list is not all-inclusive, as any deviation from the manufacturer's instructions make the test a modified FDA approved method, and therefore subject to VER 5-11, as well as high complexity personnel requirements:

- Change in specimen handling instructions;
- Using a different sample matrix (e.g.plasma vs urine);
- Incubation times or temperatures;
- Change in specimen or reagent dilution;
- Using a different calibration material (or changing the manufacturer's set points);
- Using a different antibody (source, monoclonal-vs.-polyclonal);
- Change or elimination of a procedural step;
- Change or addition of detector (conjugate) or substrate;
- Change in the solid phase;
- Change in the cutoff or method of calculating the cutoff for semi-quantitative assays;
- Change in the endpoint or calculation of the endpoint;
- Addition of adsorbent;
- Change in the strain or antigen in serologic assays;
- Changing the type of analysis (e.g. qualitative results reported as quantitative); and
- Using the test for purposes other than the manufacturer's stated intended use.

Prior to patient testing, have each of the following performance specifications been established and documented for each non-waived test or method: (VER 5 – 11)

VER 5 R

Accuracy?

The real value of the substance tested is obtained.

VER 6 R

Precision?

The same number is obtained upon repetitive testing.

VER 7 R

Reportable range?

The range is from the value of the minimum calibrator to the value of the maximum calibrator. The range is from the lowest to highest value for which the laboratory can verify the accuracy of the test system. The reportable range for patient results cannot exceed the highest or lowest value of the known standard used to verify the test system. Patient results which exceed this range (either high or low) must be reported as greater than or less than the maximum or minimum standard value unless another procedure has been developed to adjust for specimens beyond the maximum range.

VER 8 R

Reference range?

The range of values expected for a given population.

VER 9 R

Analytical sensitivity?

The lowest level at which a test method can detect the analyte in a specimen being tested.

VER 10 R

Analytical specificity, including evaluation of potential interfering substances?

Analytic specificity is the ability of any test to be substance-specific, measuring the desired analyte (test substance) without detecting other similar or interfering substances that you do not want to measure.

VER 11 R

Any other performance characteristics required for test performance including linearity?

VER 11.1

Has the laboratory established requirements for specimen acceptability, including storage temperature and specimen age requirements?

The test procedures must include criteria for specimen rejection, including specimen transport, storage, and age limitation criteria established by the laboratory and approved by the Laboratory Director.

VER 11.2

As part of the method validation, has the laboratory evaluated the potential risk of carryover between samples, and does the procedure include identification, investigation, and correction of errors due to carryover?

C) Applicable to All Non-Waived Methods

Prior to patient testing, have each of the following performance specifications been verified and documented for each non-waived test or method. (VER 12-14)

VER 12 R

Have you determined appropriate calibration and quality control frequencies based upon the test system's performance specifications?

Calibration may be required more often than every six months, depending on the stability of the test system. Criteria CA 2-7 also apply. Monitor the adequacy of these frequencies in providing quality test results as a part of your Quality Assessment Plan.

VER 13 R

Are the established reference (normal) ranges for all patient tests appropriate for the laboratory's patient population?

As part of the validation process for implementation of non-waived tests and/or methods, the laboratory will need to verify the appropriateness of reference ranges. Consider the patient population served by your laboratory. What factors are present in the patient population that could have an impact on reference ranges, such as age, ethnic background, environmental factors such as elevation, disease states or treatment plans such as oncology and chemotherapy?

Once reference ranges are established, the laboratory will want to monitor the ranges as part of its quality assessment program.

VER 14 R

Does the laboratory take and document all corrective actions taken when test systems do not meet performance specifications verified or established by the laboratory?

VER 15 R

Are all studies for the verification or establishment of performance characteristics performed by the laboratory's own personnel and evaluated and approved by the Laboratory Director or designee prior to implementation of the test?

It is acceptable for the vendors to provide samples for these purposes, but the actual testing must be performed by the laboratory's own personnel. The results must be evaluated for acceptability by the Lab Director or designee, and approval must be documented. This applies to FDA-approved methods, modified FDA-approved methods, non-FDA approved methods, and Laboratory Developed Tests (LDT).

VER 16 R

For non-FDA approved methods, has the laboratory established performance specifications for each specimen matrix that will be tested?

Each type of specimen for testing must have performance characteristics established individually.

EVALUATION GROUPING: Calibration

This activity is included in the Analytic Phase. Calibration is the process of method standardization. It is performed according to manufacturer's instructions, or as determined by the laboratory during verification or establishment of performance specifications. Calibration is performed by using calibrators (standards) of the number, type, and concentration specified by the manufacturer to actually set parameters in the instrument which will be used as the basis for determining all other test results.

Some tests which do not require calibration are:

- Microscopic tests and manual tests (e.g. manual differentials or microbiology susceptibility tests) not performed using an instrument
- Most Prothrombin Time devices
- Some point-of-care or unit-use devices which are factory calibrated and do not permit user calibration, or calibration is performed internally by the instrument.

Calibration Verification

Calibration verification is intended to confirm that the calibration setting continues to provide accurate results over the reportable range of the test system. It requires a minimum of three (3) samples, (low, mid-point, and high). These samples must have known values and must be tested in the same manner as patients. The results obtained are then compared to the known values and must be within established acceptable limits. If the calibration is stable, the recovered value should match the expected value. If not, troubleshooting, corrective action, and recalibration is indicated.

Calibration verification may be used to verify that a new lot of reagents, a complete change of reagents, or instrument service of critical parts has not altered the calibration. It may also be helpful in troubleshooting unacceptable QC results.

There are some exceptions to calibration verification. For example, for automated cell counters, calibration verification requirements are met if the lab follows manufacturer's instruction for instrument operation and performs a minimum of two (2) levels of QC each day of testing.

CALIBRATION

CA 1 R

For all non waived tests and methods, as applicable, is calibration performed at the frequency recommended by the manufacturer or at the frequency determined by the laboratory if more stringent than the manufacturer? Calibration is the process of method standardization according to manufacturer's instructions or as determined by the laboratory during verification of performance specifications. This is performed by using calibrators (standards) of the number, type and concentration indicated by the manufacturer to actually set parameters in the instrument as the basis of determining all other test results. Automated cell counters must be calibrated at least every six months.

EXCEPTIONS:

- Microscopic tests, and manual tests (e.g. manual differentials or microbiology susceptibility tests) not performed on an instrument do not require calibration.
- For most prothrombin time devices, calibration is not practical.