The University of Iowa | State Hygienic Laboratory

CLIA CORNER

State Hygienic Laboratory at The University o f Iowa — Third Quarter 2019

In this issue:

"If we add a new analyte to our chemistry analyzer, do we need to perform a linearity?"

"How many positive and negative samples do I need to run when implementing a new respiratory panel on a molecular method?"

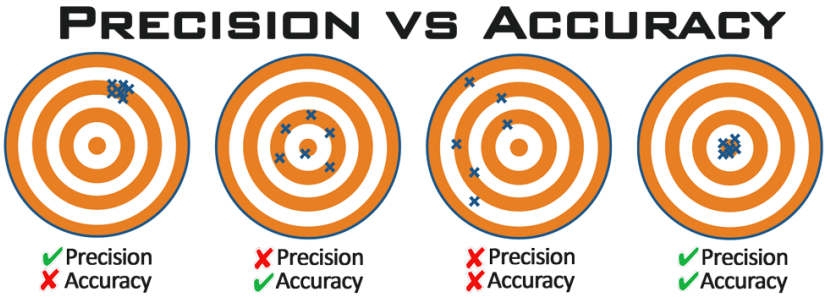
Q: What are the CLIA requirements for adding a new analyte to an existing test system?

A: **This is a trick question! The requirements for adding a new analyte to an existing test system are exactly the same as establishing and verifying the performance specifications of a new test system.**

Unmodified FDA-cleared analyte or test system

The FDA has the responsibility to classify each analyte and/or test system as either waived, moderate or high complexity. It is then the laboratory's responsibility to follow the manufacturer's instructions when performing the test. As long as the laboratory follows the manufacturer's instructions, it is considered an unmodified FDA-cleared analyte and/or test system. When adding an unmodified FDA-cleared analyte to an existing testing system or when bringing a new test system into the laboratory; the laboratory must always verify the performance specifications of accuracy, precision, reportable range, and reference range.

Accuracy – The laboratory is responsible for verifying that the method produces correct results. Verification of accuracy may be accomplished by:



- Testing reference materials;
- Comparing results of tests performed by the laboratory against the results of a reference method; or
- Comparing split sample results with results obtained from another method, which has already been shown to provide accurate results.

For qualitative methods, the laboratory must verify that a method will identify the presence/ absence of the analyte.

"We recently went live with our analyzer to perform Lyme testing. What records will you want to see?"

"Is it acceptable to use the manufacturer's reference ranges?"

"Can I report test results that are higher than my established reportable range?"

Unmodified FDA-cleared analyte or test system continued...

Precision – Precision is the same as reproducibility. The laboratory is responsible for verifying the precision of each test by assessing the day-to-day, run-to-run, and within-run variation, as well as operator variance. Operator variance is different testing personnel performing the testing at different times and receiving the same results. This may be accomplished by:

- Repeat testing of known patient samples over time;
- Testing quality control material in duplicate and over time; or
- Repeat testing of calibration material over time.

Reportable Range – Also referred to as linearity, the laboratory is responsible for verifying the reportable range of patient test results for each test system. This determines the lowest and highest result values that can be reported by the laboratory. Verification of reportable range may be accomplished by:

- Assaying low and high calibration materials or controls; or
- Evaluating known samples of abnormally high and abnormally low values.

The laboratory may only report patient test results that fall within the verified levels. The reportable range may be expanded over time, but should not exceed the manufacturer's established ranges.

Reference Range – The laboratory must verify the normal range(s) for the laboratory's patient population. The laboratory may use the manufacturer's reference range, provided it is appropriate for the laboratory's patient population. If the manufacturer has not provided reference ranges appropriate for the laboratory's patient population, the laboratory may use published reference ranges. An appropriate number of specimens must be used to verify the manufacturer's claims for normal values or, as applicable, the published reference ranges.

Modified FDA-cleared or Non-approved FDA analyte or test system

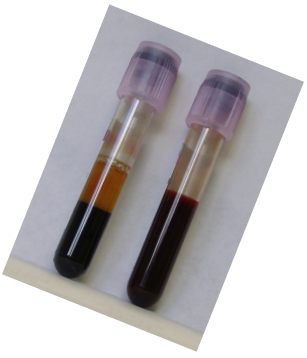
If an analyte and/or test system is not categorized (or approved) by the FDA, it automatically becomes a high complexity test. This would include laboratory developed tests. An analyte and/or test system is considered modified by the laboratory when any change occurs that could affect its performance specifications for sensitivities, specificity, accuracy, or precision. Examples (not all inclusive) of modifications to an analyte and/or test system include:

- Change in specimen handling instructions;
- Change in incubation times or temperatures;
- Change in dilution of specimen or reagent;
- Using a different calibration material or reference material, or changing the manufacturer's set-points;
- Change or elimination in procedural step;
- Change or addition of a detector (conjugate) or substrate;
- Change in the cutoff or method of calculating the cutoff for semi-quantitative assays;
- Using a different sample matrix (plasma vs urine);
- Using or promoting the test for another purpose (screening vs diagnostic); and
- Changing the type of analysis (qualitative vs quantitative).

A waived or moderate complexity test that has been modified (including modifications in its intended use) are considered uncategorized for CLIA purposes and therefore become high complexity tests.

For a modified FDA-cleared or non-approved FDA analyte and/or test system the laboratory must establish the performance specifications of accuracy, precision, reportable range, and reference range. In addition, the laboratory must also establish the performance specifications of analytical sensitivity and analytical specificity.

Analytical Sensitivity – The laboratory is responsible for determining the lowest concentration or amount of the analyte (substance) that can be measured or distinguished from a blank, i.e., minimum detection limits or how much of the analyte must be present to be measured. For modified test systems, the laboratory may use the lower limit of the manufacturer's reportable range if the laboratory has demonstrated that the modification has not affected the lower limit.



Analytical Specificity – The laboratory must determine the extent to which the method measures the analyte for which it is reporting results. It must document information regarding interfering substances from product information, literature, or its own testing data. This would include the effects of specimen hemolysis, anticoagulant, lipemia, and turbidity; patients' clinical conditions, disease states, and medications.

Additional Requirements

Review and Approval – The laboratory director or designee must review and approve the performance specification records prior to the new analyte and/or test system being put into use.

Training & Competency – When new analytes and/or test systems are introduced into the laboratory, prior to reporting patient test results, all personnel must receive and document appropriate training for the new analytes and/or test system.

Procedure – A written procedure, approved by the laboratory director, must be in place prior to reporting patient test results. The manufacturer operator's manual or package insert may be used as the procedure as long as the laboratory adds any component of the procedure not provided by the manufacturer.

Proficiency Testing (PT) - For regulated analytes, the laboratory must enroll in an approved PT program. For unregulated analytes, the laboratory must verify the accuracy at least twice annually. One way this can be accomplished is by enrolling in PT for unregulated analytes. *Remember, if the laboratory has previously performed testing but is changing to a different methodology, the laboratory will need to notify the PT company of the change in test systems/methodology.*

Laboratory Information System (LIS) and Test Reports – The laboratory must ensure that the correct units of measure and reference ranges are updated in the LIS. It must also ensure that test results are accurately and reliably being sent from the point of data entry to the final report destination. If the LIS performs a calculation to determine the test result, the calculations must be verified prior to releasing patient test results.

For non-FDA approved or modified tests the laboratory must include a statement on the test report similar to: "The performance characteristics of this test were determined by (name of facility). It has not been cleared of approved by the US Food and Drug Administration."

Conclusion

Laboratories do a great job implementing new test systems into the laboratory. This is, in part, due to instruction and help from the manufacturer. However, we have discovered when a laboratory adds a new analyte to an existing test system one or more of the above steps is frequently overlooked. Remember the CLIA requirements are the same when adding an analyte to an existing test system as it is when implementing a completely new test system!

Reference

- State Operations Manual, *Appendix C- Survey Procedures and Interpretative Guidelines for Laboratories and Laboratory Services*; Centers for Medicare and Medicaid Services (CMS); published January 12, 2004.

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