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Laboratory Developed Tests

● Introduction ●

All of these definitions, from various sources, are used to describe laboratory developed tests (LDTs):

- Tests developed in-house that are not commercially available
- Tests which have been developed, from the ground up, by a laboratory, and cannot be purchased as kits or prepared reagent sets from suppliers
- A type of in-vitro diagnostic test that is designed, manufactured and used in a single CLIA-certified laboratory, as opposed to a commercially distributed test, which is manufactured and sold for use by many laboratories
- Tests that are manufactured and interpreted by the same individual laboratory that designed them
- Tests that hospitals, academic and clinical laboratories develop as testing services according to their own procedures.

These in-house created laboratory tests are sometimes called “home-brew” tests. They allow a clinical laboratory to perform a desired test to meet specific needs when no commercially available test exists. LDTs may be used to:

- Allow diagnosis of relatively rare diseases
- Meet the needs of a local or specific population
- Advance the growth of personalized medicine
- Provide a cost savings.

The Food and Drug Administration (FDA) regulates medical devices, including in vitro diagnostic devices (IVDs). Test systems, reagents and instruments used for laboratory testing are considered IVDs. The device manufacturer must meet the FDA requirements before it can sell test systems for use by clinical laboratories. For FDA approval of commercially available IVDs, the FDA reviews both analytical validity and clinical validity before the test becomes available for sale and use.

Clinical laboratories that perform testing using these IVDs are regulated by the Centers for Medicaid and Medicare Services (CMS) via the CLIA program, which focuses on test accuracy and reliability. CLIA allows laboratories to modify FDA-approved tests and to develop their own tests, but the laboratory must validate the analytic test performance before testing patients. The CLIA program requires analytical validation only and does not address clinical validity in the regulations. Confirmation of this analytical validity will be made at the time of the onsite regulatory inspection, most likely after patient testing has already begun.

By default, since LDTs are not evaluated or categorized by the FDA, all LDTs are categorized as high complexity. This means that any laboratory that performs LDTs must meet all CLIA requirements for high complexity testing.

● Implications of High Complexity Status ●

Laboratories performing LDTs must meet all personnel requirements for laboratories performing high complexity testing. This means the laboratory must have a Laboratory Director, Clinical Consultant, Technical Supervisor (for each high complexity specialty) and General Supervisor that meet the CLIA personnel qualifications for these positions; and that all Testing Personnel who perform high complexity testing must be qualified to do so. Each individual must fulfill their CLIA-defined responsibilities. The relevant CLIA regulations for high complexity personnel are 42 CFR 493.1441 to 493.1495.

● Method Validation Requirements ●

Laboratories performing LDTs must establish and validate all performance specifications for the test before initiating patient testing. This process provides evidence that the method's performance meets the needs of the clinicians and clients. Before beginning, each laboratory must create a validation plan which includes what performance specifications will be evaluated, what samples will be included in the validation testing, when and how the samples will be tested, how the data obtained will be evaluated and the criteria to be used to determine if the data obtained is acceptable. It's important to ensure the acceptability criteria used ensures the test is meeting the laboratory's expectations and the clinical needs for the individuals' using the results.

The performance specifications that must be established to ensure analytical validity are:

- Accuracy: How close a test result is to the true value. For quantitative tests, the laboratory must verify that the test gives the correct results with the personnel and equipment to be used. For qualitative tests, the laboratory must verify that the test correctly identifies the presence or absence of the analyte.
  Standard curves used to obtain quantitative results must be performed with each sample run. Alternatively, the laboratory may establish a frequency for standard curve testing and demonstrate the accuracy of quantitative results for the established frequency.
- Precision: The degree to which repeated test results on the same sample agree; the within-laboratory reproducibility of the test. The laboratory must verify that the results are reproducible, even when different testing personnel perform the test.
- Sensitivity: The lowest level of the analyte that the test method can accurately detect.
- Specificity: The ability of the test to detect and measure the desired analyte without detecting other similar substances that should not be measured, and without being affected by interfering substances.
- Reportable range: The lowest and highest result the test can accurately measure based on the value of the minimum and maximum value of calibrators or known standards. The laboratory must determine the reportable range and may only report results that fall within the established upper and lower limits. A policy must be established for how the laboratory will report results that are higher or lower than the values at the end of each range.
- Reference range: The span of values for the test representing the results the laboratory would expect to see in healthy (normal) individuals. Reference ranges establish the normal values for the laboratory's patient population and should reflect any applicable medical decision limits for clinicians.

- Specimen acceptability: The storage temperature and specimen age requirements for each specimen type and/or collection device. The established specimen acceptability requirements must be determined for the laboratory's test method using patient samples stored at the desired conditions.
- Any additional performance specifications based on the testing specialty and unique aspects of each LDT. All LDT method characteristics (e.g., carryover, matrix effect, fluorescent dye cross-reactivity, reagent storage) must be evaluated.

The relevant CLIA regulations for establishment of performance specifications are 42 CFR 493.1253 (b) (2).

All changes to the established LDT test method (eg, new or additional instrument, new sample type, change in reagent) must be validated. The laboratory is required to re-establish all performance specifications which may be impacted by the change(s) made.

● Method Validation Documentation ●

The laboratory must maintain all validation documentation in an organized fashion. The completed documentation must include the laboratory's method information including but not limited to:

- Instrumentation used including name and serial number
- Instrumentation settings specific for the method
- Other equipment used (e.g., pipettes, centrifuges, etc.)
- Reagents used including manufacturer, catalog numbers and lot numbers
- Disposable items used (e.g., 96-well plates, specimen vials, etc.)
- Overview of the testing process
- How the patient data will be analyzed to produce a reportable result (if applicable)
- Criteria used to demonstrate validity of the reportable result (if applicable)

The compiled validation summary must be approved by the laboratory director or qualified designee and include the following information at a minimum:

- Intended use
- All accepted specimen types and collection devices
- Reference material / standard information (e.g., manufacturers, catalog numbers)
- Detailed description how each performance specification was evaluated including:
    - Reference materials or patient samples used
    - When and how the samples were tested
    - A summary of the data obtained
    - An explanation of how the data was analyzed
    - The criteria used to determine if the data obtained is acceptable
    - An explanation for any obtained data which does not meet the laboratory's established acceptability criteria but is deemed acceptable by the laboratory director

Raw data from the validation is not required to be included in the validation summary but must be retained and available for as long as the test system is in use plus an additional two years.

● Calibration and Quality Control ●

Appropriate calibration and quality control methods and frequencies must be established for LDTs. At a minimum, adhere to the CLIA regulatory requirements for calibration, calibration verification and for performing two levels of quality control each day of testing. The relevant CLIA requirements for calibration and calibration verification are 42 CFR 493.1255, and for quality control are 42 CFR 493.1256.

Implementing the concepts of Individualized Quality Control Plans (IQCP) is an excellent option for evaluating risk with LDTs. IQCP utilizes risk assessment to identify actual and potential risks in all phases of testing, and to mitigate those risks to prevent errors. The laboratory must adhere to the CLIA QC requirements at the minimum , but IQCP can help the laboratory determine if that amount of QC is adequate or if additional QC is necessary to fully mitigate risks associated with an LDT.

● Equipment maintenance and function checks●

The laboratory must establish procedures for maintenance and function checks of all equipment involved in the testing process, to be performed at a frequency that ensures accurate and reliable test performance.

Over time, calibration, quality control and maintenance frequencies may need to be adjusted as more data is compiled about the ongoing performance and stability of the method.

● Specimen integrity criteria ●

Criteria to ensure integrity of the specimens that will be tested must be established, including:

- Acceptable specimen types and volume needed for testing
- Specimen collection, including patient preparation and identification procedures
- Specimen identification through all phases of testing
- Specimen age limits for testing
- Specimen storage and transport temperatures
- Specimen rejection criteria.

• Laboratory reports •

Reports for LDTs must include:

- A statement indicating that the performance specifications for the test were established by the laboratory AND
- A statement indicating that the test methodology has not been cleared or approved by the FDA.

• Best practices •

Laboratory Developed Tests do not have the benefit of the rigorous evaluation by the FDA before being used for patient testing. Keeping that in mind, it is wise to consider doing more than the minimum when validating the test and when performing ongoing quality control, maintenance procedures and quality assessment activities. Make it robust to ensure quality results!

- Your laboratory needs to have a written procedure that describes how the validation studies were performed. Include criteria for acceptability and keep the raw data, conclusions and laboratory director approval.
- Develop and maintain a detailed procedure manual for the test.
- Enroll in proficiency testing if a suitable module exists or develop a split-sample testing protocol to help confirm test accuracy and reliability.
- Retain detailed documentation of all test activities.

• Potential issues •

Problems can occur and inspections can yield citations when:

- The laboratory director does not qualify to direct high complexity testing
- The technical supervisor does not have the experience to meet the specialty/subspecialty requirements for the tests being performed
- Testing personnel do not qualify to perform high complexity testing. Keep in mind that specimen preparation is part of the high complexity process and personnel must qualify.
- Validation of performance specifications is not detailed enough to demonstrate the accuracy and reliability of the method
- Validation studies and associated data are not adequately documented and retained for as long as the test is in use (and for 2 years after discontinuation).

The requirements stated above also apply to any FDA-approved test that has been modified by your laboratory. When an FDA-approved test is modified, the test becomes high complexity and essentially turns into an LDT.