

CLIA Overview...

What is CMS' authority regarding Laboratory Developed Tests (LDTs) and how does it differ from FDA's authority?

The Clinical Laboratory Improvement Amendments (CLIA) program regulates laboratories that perform testing on patient specimens in order to ensure accurate and reliable test results. The FDA regulates manufacturers and devices under the Federal Food, Drug, and Cosmetic Act (FFDCA) to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective.

The FDA defines a Laboratory Developed Test (LDT) as an *in vitro* diagnostic test that is manufactured by and used within a single laboratory (i.e. a laboratory with a single CLIA certificate). LDTs are also sometimes called in-house developed tests, or "home brew" tests. Similar to other *in vitro* diagnostic tests, LDTs are considered "devices," as defined by the FFDCA, and are therefore subject to regulatory oversight by FDA.

When a laboratory develops a test system such as an LDT in-house without receiving FDA clearance or approval, CLIA prohibits the release of any test results prior to the laboratory establishing certain performance characteristics relating to analytical validity for the use of that test system in the laboratory's own environment, *see* 42 CFR 493.1253(b)(2) (establishment of performance specifications). This analytical validation is limited, however, to the specific conditions, staff, equipment and patient population of the particular laboratory, so the findings of these laboratory-specific analytical validation are not meaningful outside of the laboratory that did the analysis. Furthermore, the laboratory's analytical validation of LDTs is reviewed during its routine biennial survey – after the laboratory has already started testing.

In contrast, the FDA's review of analytical validity is done prior to the marketing of the test system, and therefore, prior to the use of the test system on patient specimens in the clinical diagnosis/treatment context. Moreover, the FDA's premarket clearance and approval processes assess the analytical validity of a test system in greater depth and scope. The FDA's processes also assess clinical validity, which is the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient, as part of the review that is focused on the safety and effectiveness of the test system. Furthermore, unlike the FDA regulatory scheme, CMS' CLIA program does not address the clinical validity of any test.

Thus, the two agencies' regulatory schemes are different in focus, scope and purpose, but they are intended to be complementary.

Laboratory Developed Tests (LDTs) Frequently Asked Questions

1. What is a Laboratory Developed Test?

The FDA defines a Laboratory Developed Test (LDT) as an *in vitro* diagnostic test that is manufactured by and used within a single laboratory (i.e. a laboratory with a single CLIA certificate). LDTs are also referred to as in-house developed tests or “home brew” tests.

2. What is the difference between the CMS’ authority versus FDA’s authority regarding LDTs?

The Clinical Laboratory Improvement Amendments (CLIA) program regulates laboratories to ensure accurate and reliable test results when laboratories perform testing on patient specimens. The FDA regulates manufacturers and devices under the Federal Food, Drug, and Cosmetic Act (FFDCA) to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective.

Similar to other *in vitro* diagnostic tests, LDTs are considered “devices,” as defined by the FFDCA, and are therefore subject to regulatory oversight by FDA. Although the FFDCA requires manufacturers of all *in vitro* diagnostic devices (IVDs), including LDTs, to comply with the regulatory requirements governing device safety and effectiveness (such as quality controls for device design and other aspects of device manufacturing, premarket clearance/approval, etc.), the FDA has generally exercised enforcement discretion so that the agency has generally not enforced these requirements for LDTs. LDTs, therefore, generally have not undergone FDA premarket review, which assures both the analytical validity (e.g. analytical specificity and sensitivity, accuracy and precision) and clinical validity of IVDs.

Under the CLIA regulations, when a laboratory uses a test system that has not received FDA clearance or approval, such as a LDT, the laboratory may not release any test results prior to establishing certain performance characteristics relating to analytical validity for the use of that test system in the laboratory’s own environment, *see* 42 CFR 493.1253(b)(2) (establishment of performance specifications). CLIA and its implementing regulations do not affect FDA’s authority under the FDCA to regulate LDTs or other devices used by laboratories.

Further, CMS’ CLIA program does not address the clinical validity of any test – that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. On the other hand, FDA evaluates the clinical validity of a test under its premarket clearance and approval processes and as a result, has expertise in this area. In other words, the FDCA encompasses clinical validity whereas CLIA does not.

Thus, the regulatory schemes of the two agencies are different in focus, scope and purpose, but the two schemes are intended to be complementary.

3. What does CMS CLIA require for analytical validity for LDTs?

The analytical validation under CLIA looks at the performance characteristics of a test used to describe the quality of patient test results, and includes an analysis of accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference interval, and any other performance characteristics required for the test system in the laboratory that intends to use it. This analytical validation is limited to the specific conditions, staff, equipment and patient population of the particular laboratory, so the findings of these laboratory-specific analytical validation are not meaningful outside of the laboratory that did the analysis.

4. What is the difference between the CMS' analytical validity review versus the FDA's analytical validity review for LDTs?

The CMS' analytical validity review is intended to determine if a specific test finds what it is supposed to find (i.e. the analyte it is intended to detect) when laboratories perform testing on patient specimens. Therefore, the analytical validation must be performed by the laboratory intending to use the test on patient specimens. Furthermore, the laboratory's analytical validation of a LDT is reviewed during its routine biennial survey – after the laboratory has already started testing. Moreover, the routine CLIA survey does not include a review of the clinical validation of a LDT – that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient.

In contrast, the FDA's review of analytical validity is done prior to the marketing of the test system, and therefore, prior to the use of the test system on patient specimens in the clinical diagnosis/treatment context. Further, the FDA's analytical validity review is more in-depth and more comprehensive than that of the CLIA program, and it is focused on the test system's safety and effectiveness. As a result, FDA review may uncover errors in test design or other problems with a test system. Also, while CMS' CLIA program does not address the clinical validity of any test, FDA's premarket review of a test system includes an assessment of clinical validity.

5. What does CMS CLIA require for laboratories performing LDTs?

The CLIA requirements are based on the test complexity; the more complex the test is to perform, the more stringent the requirements. LDTs are considered high complexity tests. Therefore, the laboratory must meet all applicable CLIA requirements for high complexity testing.