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Regulatory Knowledge Guide for Laboratory Developed Tests

NIH SEED Innovator Support Team

Introduction

Laboratory developed tests (LDTs) have a fundamental role in the U.S. healthcare system. Whether they are standard flu tests, emerging pathogens tests, or rare disease tests, they can provide clinicians and consumers essential information in the diagnosis and treatment of disease.

LDTs are a specific type of ***in vitro* diagnostic** (IVD). An *in vitro* diagnostic is a medical device regulated by the U.S. Food and Drug Administration (**FDA**). The term "*in vitro*" refers to processes that take place in a test tube rather than in or on a living organism. An IVD is intended to be used for the collection, preparation, and examination of specimens *taken from the human body*. IVDs are used to diagnose a disease or to monitor and treat other health conditions.

An LDT is a type of IVD that is completely designed, manufactured, and used within a single laboratory. Several factors can affect whether a new product is an LDT, including the test's intended use, patient population, claims, manufacturing, labeling, and marketing plans. LDTs are considered devices under the Federal Food, Drug, and Cosmetic Act and fall under regulatory oversight of FDA.

The regulation of LDTs is complex and evolving. Even though LDTs are a subset of IVDs, innovators must use caution because there are several differences between the regulation of IVDs and LDTs (see the Appendix). Congress has for the past decade introduced—but never enacted—legislation to clarify the regulatory path for LDTs. As a result, many LDTs continue to be regulated under the original FDA enforcement discretion policy, which means that FDA has generally not enforced premarket review and other applicable FDA requirements for LDTs. Furthermore, some tests, such as direct-to-consumer (**DTC**) tests, (blood) donor screening, as well as tests intended for emergency use are deemed higher

risk by FDA and do not fall under enforcement discretion (regardless of whether they meet the definition of an LDT) and must be reviewed by FDA before bringing them to market.

In 2023, FDA proposed a new rule regarding LDTs that, if passed, would amend the definition of IVD products to include LDTs. It would also phase out FDA's general enforcement discretion approach.

Most LDTs in development will not require FDA premarket approval because they fall under "enforcement discretion."

While LDTs are considered devices and fall under regulatory oversight of FDA, laboratories developing and performing the LDT are regulated by the Centers for Medicare & Medicaid Services (CMS) through the **Clinical Laboratory Improvement Amendments** (CLIA) program. CLIA regulations do not impact FDA's authority to regulate LDTs. Since LDTs are not only designed but also performed in a single clinical laboratory, it is important to consider regulatory oversight for the test itself (FDA) and for the laboratory (CMS/CLIA) in which LDTs are performed.

Some innovators may try to use the LDT pathway as a less costly and time-consuming regulatory route than seeking FDA-approval/clearance to bring their products to market. In some cases, that may be a perfectly appropriate path. But FDA's concern about the safety and efficacy of many LDTs is a factor and will impact whether a development plan via the LDT pathway is realistic.

This Regulatory Knowledge Guide prepares innovators to develop and market a test as an LDT. To make it easier to determine if your product should use another pathway, this guide includes a list of several instances in which tests may look like an LDT, but on closer inspection do not meet FDA's strict definition and thus should go to FDA for premarket review.

Please use the Word navigation panel to jump to sections that are relevant for your specific needs. Bolded terms within the text are defined in the Glossary.

If you have questions about the LDTs, the NIH Office of Extramural Research (OER) Small Business Education and Entrepreneurial Development (SEED) team recommends you contact the SEED Innovator Support Team.

After reading this Regulatory Knowledge Guide, you will have a better understanding of how to develop and offer a test as an LDT.

- An LDT is a type of *in vitro* diagnostic that is completely designed, manufactured, and used within a single laboratory (with a single CLIA Certificate).
- For many years, FDA has exercised "enforcement discretion" over LDTs. This means that FDA does not intend to enforce regulatory requirements for this specific type of device.
- Laboratories developing and performing the LDT are regulated under the CLIA program. CLIA regulations do not impact FDA's authority to regulate LDTs.
- IVDs (including LDTs) are not permitted to use therapeutic product information as part of their test descriptions and/or intended use statements without seeking FDA approval as a companion diagnostic.
- Labs performing LDTs (which are considered high complexity tests) must adhere to stringent CLIA requirements prior to the tests being used on patients.
- Certain tests that meet the definition of an LDT—that is, they are designed, manufactured, and used within a single laboratory—are nonetheless required to obtain FDA premarket approval, if they have a higher risk profile or do not fall under FDA enforcement discretion.
- FDA generally does *not* exercise enforcement discretion for direct-to-consumer or (blood) donor screening tests, as well as tests intended for emergency use regardless of whether they meet the definition of an LDT.
- Laboratories serving patients from other states (i.e., samples are collected from patients that reside outside the state where the lab is located) may have to also obtain certain state-specific lab permits from the state's Health Department.

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1 Oversight and Regulation

The regulation of laboratory developed tests (LDTs) is complex and evolving. While LDTs are considered devices (which fall under regulatory oversight of the Food and Drug Administration [FDA]), the laboratories that create and perform LDTs are regulated under the **Clinical Laboratory Improvement Amendments** (CLIA) program.

Under the CLIA, FDA, Centers for Medicare & Medicaid Services (CMS), and Centers for Disease Control and Prevention (CDC) share responsibilities for oversight of LDTs to ensure high-quality diagnostic laboratory testing. CLIA regulations do not impact FDA's authority to regulate LDTs.

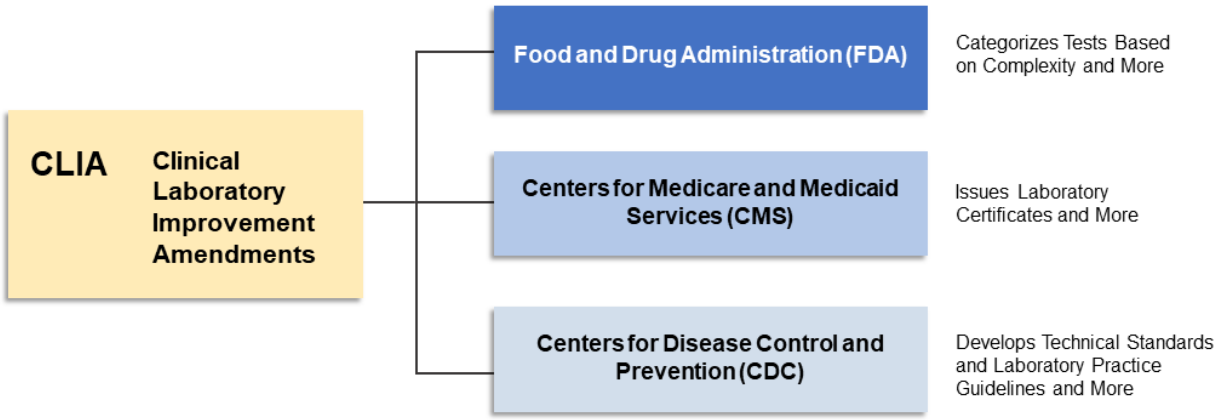


Figure 1. Multiple agencies share authority to implement CLIA regulations

Recognizing that many LDTs on the market today have never been cleared or approved by FDA, Congress has, for the past decade, introduced—but never enacted—legislation to clarify the regulatory path for LDTs. As a result, many LDTs continue to be regulated under the original enforcement discretion policy, which means that FDA has generally not enforced premarket review and other applicable FDA requirements for LDTs. Over time, FDA has also limited the enforcement discretion policy through releasing guidance on related issues (e.g., direct-to-consumer testing and companion diagnostics).

Innovators should be aware that the regulations related to LDTs continue to evolve. The regulatory status of LDTs changed several times during the COVID-19 public health emergency and remains uncertain. When developing a new LDT or expanding it, innovators are advised to contact the NIH OER SEED Innovator Support Team for the most up-to-date guidance on current regulations.

Resources:
FDA: Framework for Regulatory Oversight of 8 Laboratory Developed Tests
FDA: Devices@FDA Database

HHS: [CMS Authority Regarding Laboratory Developed Tests]

2 Definition of an LDT

Although an LDT is currently under enforcement discretion, it is possible that FDA could change policy and choose to regulate it in the future. The term enforcement discretion means that even though FDA has authority to regulate all medical devices (including LDTs), it may decide not to do so. Currently, most LDTs continue to be under FDA enforcement discretion.

Examples of LDTs under enforcement discretion include tests developed in hospital laboratories and used for testing patients within the lab's health system. These may include:

- COVID-19 (infectious disease) assays
- Esoteric tests and rare disease assays
- Emerging pathogens assays
- Vitamin D assays
- Drug tests
- Flu tests

2.1 Development in Single Laboratory

Tests that are completely designed, manufactured, and used within a single clinical laboratory are LDTs (with a single CLIA certificate). In addition, these tests must only be used by a laboratory that meets the requirements for high complexity testing under CLIA as described in 42 CFR 493.17(c)(4) and 493.25.

FDA does not consider devices to be LDTs if they are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them.

FDA does not consider the following to be LDTs

- **An entity that owns several clinical laboratories (with separate CLIA certificates) develops a device in one of its clinical laboratories, and then transfers the device to several clinical laboratories within its network.**
- **An academic institution develops a device, which it then licenses to or signs an exclusivity agreement with a private corporation that owns a CLIA-certified laboratory. The private corporation's CLIA-certified laboratory then begins manufacturing and using the device to provide clinical diagnostic results.**
- **A clinical laboratory develops a device and sells/licenses it to a third-party lab in addition to using it in-house.**
- **A clinical laboratory contracts with a third-party manufacturer to produce a key component (e.g., coated microtiter plate, specialized specimen collection kit) used in its device.**
- **A clinical laboratory contracts with a specification developer to design a new device. Once complete, the design is then transferred to the clinical laboratory for final validation prior to the device being manufactured and used by the laboratory to provide clinical diagnostic results.**

Resource:
FDA: Laboratory Developed Tests
FDA: Discussion Paper on Laboratory Developed Tests (LDTs)
FDA: The Public Health Evidence f or FDA Oversight of Laboratory Developed Tests: 20 Case Studies
CRS: HHS Announcement on FDA Premarket Review of Laboratory-Developed Tests

2.2 Conceptualizing an LDT

One of the most common types of LDTs under enforcement discretion are "modified" **IVD**s. These types of LDTs were referred to as "home brew" tests in the past and are based on an FDA-approved IVDs. They are diagnostics developed within the innovator's laboratory and may include modifications to the original IVD. These tests are validated in-house (under CLIA) and answer the same questions as the IVD; they are considered an LDT and do not require FDA clearance.

If a test is designed in an academic research laboratory, but performed in a health system's clinical laboratory, the test is not an LDT. Unlike academic research laboratories, clinical laboratories must have a certificate showing that they meet federal quality standards (**CLIA)**, which are set by CMS. The CLIA's quality standards apply to the laboratory's personnel, equipment and facilities, and processes.

If a test is designed in an academic research laboratory, but performed in a health system's clinical laboratory, the test is not an LDT—even if the two laboratories are on the same university campus.

However, if you develop a test in an academic laboratory, you can turn your lab into a clinical laboratory by obtaining a CLIA certificate. Another common path is to license the test technology to another party to develop the test and bring it through FDA premarket review.

Laboratories may decide to modify one of their existing LDTs based on new scientific research. This can be done by adding or removing an **analyte** to or from a test panel. This approach does not usually impact the intended use and target patient population. However, test results and interpretations may change. In this case, labs are required to ensure that clinicians and their patients are informed about test report changes and that an updated version of the test is available.

Per CLIA, all LDTs that are used in a way that modifies the FDA-approved IVD are high complexity tests. These tests must be run in a high complexity CLIA-certified lab.

If a new LDT is based on the discovery of a novel **biomarker** for diagnosing health conditions or rare diseases, it is still considered a clinical (not research) test. As such, it must be completely designed, manufactured, and used within a single, clinical laboratory.

During the design step, the test developer will identify formal specifications for the test, including the desired performance criteria required to meet defined clinical needs, as well as the commercial and technical requirements to perform the test safely and effectively. Other important characteristics of the test include its intended clinical usefulness, such as for patient screening, diagnosis, prognosis, risk prediction, treatment selection, or treatment monitoring. Based upon the expectations of clinical performance for the intended clinical use, the test developer will next identify analytical performance specifications. Those include **analytical specificity**, detection capability, bias, **precision**, and measuring interval.

Resources:
FDA: Laboratory Developed Tests
CDC: Clinical Laboratory Improvement Amendments

2.3 Establishing Level of Risk

For LDTs, one of the most important components is to establish the **level of risk** as part of the test or product profile. Levels of risk depend on the complexity of the test and the impact results can have on patient care, e.g., potential harm of an incorrect or misinterpreted test. They can be categorized into low-, moderate-, and high-risk tests.

Risk levels differ from the complexity of a test. Risk levels refer to the potential harm an incorrect or misinterpreted test result can impose on patients; complexity levels refer to how the test is run in the lab, e.g., only highly specialized staff are allowed to perform and read the results of tests with high complexity. In addition, tests with high complexity can only be performed in a lab that is certified as a high complexity lab under **CLIA**.

2.4 Selling or Licensing

FDA does not consider a device to be an LDTs if it is designed or manufactured completely, or partly, outside of the laboratory that offers and uses them.

If any part of an LDT's underlying intellectual property is sold or licensed to another laboratory that will perform it, then the test requires FDA clearance or approval.

The examples below are categorized in FDA's 2014 draft guidance "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" as being **IVD**s that do not meet FDA's definition of an LDT and thus should come to **FDA** review.

- An entity that owns several clinical laboratories (with separate **CLIA** certificates) develops a device in one of its clinical laboratories, and then transfers the device to several clinical laboratories within its network.
- A clinical laboratory develops a device and sells/licenses it to a third-party lab in addition to using it in-house.
- A laboratory contracts with a third-party manufacturer to produce a key component (e.g., coated microtiter plate, specialized specimen collection kit) used in its device.
- A laboratory contracts with a specification developer to design a new device. Once complete, the design is then transferred to the clinical laboratory for final validation prior to the device being manufactured and used by the laboratory to provide clinical diagnostic results.

2.5 Companion Diagnostics (CDx)

A **CDx** is an **IVD** that FDA has determined to be essential to the safe and effective use of a corresponding drug or biologic. This type of test is used by healthcare providers to determine the right medication for an individual based on safety and efficacy. This is done by analyzing the individual's **biomarkers** which provide an indication if the medication is suited for them.

While many LDT innovators may plan to use their diagnostic in conjunction with a drug or biologic to offer treatment decisions for the safer use of the therapeutic, FDA approval is required in order to do so. Using therapeutic drug information is prohibited unless you have FDA approval. This is usually done via the Premarket Approval (PMA) submission pathway. (See Section 5 of the Regulatory Knowledge Guide for Therapeutic Devices.)

Only IVDs that have FDA-approval as a CDx are permitted to use therapeutic product information on their label or test descriptions.

IVDs (including LDTs) cannot use therapeutic product information as part of their test descriptions, intended use statements, or label without seeking FDA approval. This is also the case for LDTs developed based on existing **companion diagnostics**.

If you plan to use the therapeutic drug information (for which an FDA-approved test is required for the safe and effective use of the drug or biologic), it must first be approved as a CDx.

Please refer to Section 8 of the Regulatory Knowledge Guide for *In Vitro* Diagnostics for more information on the regulatory requirements for CDx.

2.6 Surveillance, Screening, or Emergency Use Authorization

Surveillance testing is performed on populations to determine incidence or prevalence of a disease or monitor community-level spread. These tests are not LDTs and do not require FDA approval. In surveillance testing, patient samples are collected but do not receive individual identifiers. The results are not linked to individual people and are only reported at a population level.

Surveillance tests are not LDTs and are not regulated by CLIA. As such, they are not required to obtain premarket approval or clearance from FDA.

Screening testing is performed on a broad set of individuals with the intent of looking for occurrence of certain diseases at the individual level. FDA exercises enforcement discretion for an LDT used as a screening test. This can include the screening of individuals even if there is no reason to suspect infection or manifestation of a disease—meaning asymptomatic individuals without known exposure to an infectious disease or individuals without known risk factors for an inherited disease (family history). In contrast to surveillance testing, this is done with the intent of making individual decisions based on the test results. Screening can assist with identifying an infected person before symptoms develop to prevent other people from getting infected; it can also assist with catching and treating a potential health concern early.

For LDTs used as a screening test, FDA has exercised enforcement discretion for state and local public health laboratories. Any time patient-specific results are reported, the facility must possess a CLIA certification or equivalent before accepting patient samples.

Emergency Use Authorizations (EUAs) are issued by FDA during a public health emergency to enable public access to unapproved devices or for unapproved uses of approved devices when certain criteria are met. Innovators developing an LDT for use during a public health emergency should consult FDA's guidance documents and templates for EUA. At the time of this writing, the FDA is requiring EUA submissions for COVID-19 LDTs. Innovators are advised to contact the NIH OER SEED Innovator Support Team the most up-to-date regulatory guidance.

Resource:
FDA: Emergency Use Authorization of Medical Products and Related Authorities
FDA: Summary of Process for EUA Issuance
FDA: Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests

2.7 Special Use Cases

FDA applies special rules to certain diagnostic tests and test components. Analyte specific reagents (ASRs) are biological molecules—such as polyclonal or monoclonal antibodies, receptor proteins, ligands, and nucleic acid sequences—when they are used as active ingredients in a diagnostic product, such as an LDT.

ASRs are labeled "for *in vitro* clinical diagnostic use" and are designed to meet FDA's quality standards for LDT components in clinical laboratories. FDA's rules state that tests or devices using ASRs cannot be labeled with instructions for use or performance claims and cannot be promoted for use on specific designated instruments or in specific tests. While they are individual reagents used in LDTs, they do not, by themselves, permit a diagnosis. In addition, ASRs must be used in analytic processes by trained personnel who validate the test's performance using **CLIA** standards prior to reporting the test results. FDA classifies ASRs into Class I, Class II, and Class III based on their risk profile and intended use. Class II and Class III ASRs must be cleared or approved by FDA before they can be marketed in the U.S.

A newly developed ASR is likely to require premarket notification (510(k)) if it will be labeled for clinical diagnostic use. ASRs intended for only research use are a different category called Research Use Only/Investigational Use Only.

If an ASR is intended to be used in clinical diagnosis, it usually follows the 510(k) regulatory pathway. Research Use Only (RUO) or Investigational Use Only (IUO) are applied to **IVD**s that are currently under development and not approved for clinical diagnostic use. Products intended for use only in research or investigational settings are not LDTs. The term RUO refers to devices that are in the laboratory phase of development. The term IUO refers to devices that are in the product testing phase of development. For tests used as RUO/IUO, the innovator should consult the Regulatory Knowledge Guide for In Vitro Diagnostics.

Innovators developing a product intended for use only in research or investigational settings are not developing an LDT. LDTs are clinical tests performed in clinical laboratories governed by CLIA.

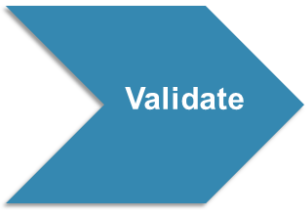
Certain tests that meet the definition of an LDT—that is, they are designed, manufactured, and used within a single laboratory—are nonetheless required to obtain FDA premarket approval, as the agency has determined that they have a higher risk profile or fall into special categories that do not qualify for enforcement discretion.

Tests Requiring FDA Premarket Review, Clearance, or Approval

- **Pharmacogenomic (PGx) tests, i.e. used to determine gene-drug interactions—also called drug metabolizing enzyme genotyping system (21 CFR 862.3360)**
- **Cancer predisposition tests/tumor associated antigen immunological test systems (21 CFR 866.6010-80)**
- **Genetic health risk tests (21 CFR 866.5950)**

Additionally, any test using home-collected specimens is not considered an LDT and must follow FDA's regulations for IVDs.

Resources:
FDA: Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions
FDA: Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only
FDA: Off-Label and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices
FDA: In Vitro Diagnostic Products



3 Validation

LDTs are, by definition, high complexity tests that must be performed in a high complexity CLIA laboratory. Prior to offering a new test to patients, the laboratory must meet all the appropriate CLIA requirements and have validated the test. See Section 4.5 for more information on high complexity standards.

Validation refers to the overall performance of the test with respect to its intended use and user needs, as well as the individual performance characteristics for each input of the test design.

LDT Validation

- **Analytical validation is required for all tests performed on patient samples, under CLIA**
- **Clinical validation is not required by CLIA, but is required by certain states (e.g., New York), and certain accreditation organizations (e.g., College of American Pathologists), and relevant documentation may be reviewed during a CLIA inspection**

3.1 Performance Characteristics, Analytes, and Protocol

Performance characteristics must be established for any test that modifies an **FDA**-cleared or -approved test system or uses a test system that is not subject to FDA clearance or approval (such as methods developed in-house). Per CLIA, they are established by the lab director at the time of assay development and include:

- **Accuracy**
- **Precision**
- **Reportable range**
- **Analytical sensitivity**
- **Analytical specificity**
- **Reference intervals**

Each of those performance characteristics is specified during the design phase, and the validation process shows whether the performance characteristics have been met. Each test must fall within the range (low, medium, high) of the pre-determined performance characteristics for the results to be valid.

When creating an LDT it is important to determining which analytes will be targeted. Analytes are substances—such as proteins, chemical compounds like glucose or cholesterol, or DNA—that can be targeted with a certain **reagent**. Different analytes require different reagents. It is essential that developers thoroughly understand the materials and substances they are using to show feasibility and optimization of the diagnostic test.

A laboratory may use peer reviewed articles to guide development of a new test protocol. Based on the intended targets of the test, the lab director selects which reagents (general purpose reagents and analyte-specific reagents) are to be used in conjunction with specific lab instruments for the test. The testing protocol is developed based on these components. The test protocol must be verified for **analytical validity** per CLIA.

Versioning of tests and test results is very important to document and track changes in data.

You have discretion to change the testing protocols for your LDT. However, keeping appropriate and accurate documentation of both tests and results is essential to the validation process.

Resource:
NIH: Validation of Laboratory-Developed Molecular Assays for Infectious Diseases

3.2 Analytical Validation

The purpose of validating a test is to optimize it for patient safety, efficacy, and intended clinical use. **Analytical validity** refers to how well a test can predict the absence, presence, or change of a particular **biomarker** (i.e., does the test find what it is intended to find).

CLIA requires that before reporting patient test results, labs must establish performance specifications used to describe a test's results.

Performance characteristics must be established for any test that modifies an FDA-cleared or -approved test system or uses a test system that is not subject to FDA clearance or approval (such as methods developed in-house).

CLIA does not require labs to establish **clinical validity** of an LDT; therefore, it is the lab's responsibility to assess whether the test provides meaningful information for clinical decision making. However, some equivalent organizations (e.g., the College of American Pathologists (CAP) and the Joint Commission) and state departments of health (e.g., New York State Department of Health) require LDTs to be clinically validated.

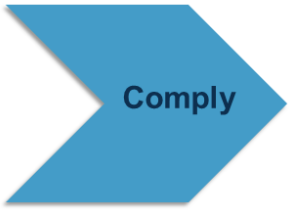
Resources:
CMS: LDT and CLIA FAQs
Article: Modernization of CLIA: LDTs

3.3 Software

The algorithms (which may be powered by Artificial Intelligence/Machine Learning) that can support LDT reporting, etc., may have many variations, parameters, and training data sets. It is important that the underlying algorithm does not change during validation because the supporting validation should reflect the version of the test being offered. It is a good practice to version and document software, like other aspects of an LDT, for quality assurance and trackability.

LDTs that include artificial intelligence algorithms should incorporate some strategy to prevent cybersecurity-related accidents or attacks that affect the test's usability or the integrity of the data. Both the U.S. Department of Health and Human Services (**HHS**), under the **Health Insurance Portability and Accountability Act** (HIPAA), and the Federal Trade Commission (FTC), under Section 5 of the FTC Act, may exercise authority over data security of health information.

For more information about FDA guidelines on cybersecurity risk mitigation plans and using artificial intelligence and machine learning in in health products, please refer to the Regulatory Knowledge Guide for Digital Health.



4 Laboratory Compliance Requirements

Before a new LDT can be used in a clinic or a lab, the lab that created the LDT must meet several specific requirements regarding inspections, **accuracy** and reliability testing, quality system monitoring, and analytic systems. Lab certification compliance is critical for LDTs.

4.1 Certification/Lab (Re)inspection

The federal government's oversight of the quality of clinical laboratory testing is divided between **FDA**, **CMS**, and **CDC**, under the law called **CLIA** (see Figure 1). CLIA standards encompass the technological capabilities of the laboratory facility itself, the processes the laboratory uses to ensure quality testing, and the training and qualifications of the laboratory director and other testing personnel. Certification can be from CMS (CLIA certification), or laboratories can obtain accreditation from a private organization selected by CMS.

As a general rule, clinical laboratories must have a current certificate of waiver, or certificate of accreditation that is applicable to the types of tests the laboratory performs.

However, CLIA regulations do not apply to certain types of laboratories, including those that only perform forensic testing, research laboratories that do not report patient-specific results of a test to inform patient care, drug testing labs that are certified by the Substance Abuse and Mental Health Services Administration, and federal laboratories.

Each laboratory issued a CLIA certificate must meet basic inspection requirements.

High complexity laboratories performing LDTs must meet additional requirements that are specific to their type of CLIA certificate.

The basic inspection process involves a visit from a **CMS** inspector. The laboratory must have all records and data available to the inspector within a reasonable timeframe and must provide the inspector with copies of all requested records and data. Reinspection usually occurs every two years and includes inspection of documents in support of tests developed since the previous CLIA inspection.

The inspector may require the laboratory to do the following:

- Test samples, including proficiency testing samples
- Permit interviews of all personnel concerning the laboratory's compliance
- Permit laboratory personnel to be observed performing all phases of the total testing process (pre-analytic, analytic, and post-analytic)
- Permit the inspector to access areas that are covered under the certificate, such as:
    - Specimen procurement and processing areas
    - Storage facilities for specimens, **reagent**s, supplies, records, and reports
    - Testing and reporting areas

Resource:
CMS: General Survey Procedures for Laboratories and Laboratory Services

4.2 Proficiency Testing

Proficiency testing (PT) is an important tool to verify the accuracy and reliability of the LDT. It is a required step for certain **nonwaived** tests (generally moderate and high complexity tests) in obtaining a **CLIA** certificate for a clinical laboratory. **CMS** and **CDC** monitor laboratory performance and practices as part of PT under CLIA.

Proficiency testing is the process of ensuring the accuracy and reliability of a new LDT. PT is also the practice of regularly testing unknown specimens sent to a laboratory from an approved entity.

The lab tests the samples and reports results back to the approved entity (under the PT program.) After submitting test results, the entity grades the results, and the laboratory receives data that compares its performance with that of other labs that used the same procedures on the same specimens. PT programs validate the testing process and lab personnel competency.

Resource:
CMS: List of Non-Waived Tests Which Require PT

4.3 Quality Systems

Each laboratory performing **nonwaived** tests (including LDTs) must have a quality system and quality control criteria in place.

CLIA requires labs to establish and maintain written quality control procedures to monitor the accuracy and precision of the total testing process (pre-analytic, analytic, and post-analytic), as well as to monitor the general laboratory systems.

The laboratory's quality control systems must include a quality assessment that ensures continuous improvement of the laboratory's performance and services through ongoing monitoring that identifies, evaluates, and resolves problems. Additionally, these quality control systems must be appropriate for the specialties and subspecialties of testing the laboratory performs, services it offers, and clients it serves. This assessment helps the lab, for instance, detect when a mistake is made during the testing process (e.g., a test result is out-of-range), understand what impact that mistake might have on clinical decision making, and determine what mitigation steps may be needed (such as issuing a revised test report).

4.4 General, Pre-Analytic, Analytic, and Post-Analytic Systems

According to CLIA requirements, clinical laboratories must have written quality control policies and procedures in place for general laboratory systems, pre-analytic systems, analytic systems, and post-analytic systems.

General laboratory systems include procedures for the following:

- Confidentiality of patient information, including compliance with related laws such as HIPAA
- Specimen identification and integrity, including special handling instructions for pathogens, and procedures for storing and transporting specimens that require special conditions of temperature, barometric pressure, or time from patient to lab
- Complaint investigations, documentation of their findings, and reporting to authorities, if required
- Communication between the laboratory and ordering providers, including procedures for alerting ordering providers of "panic values"
- Policies for assessing personnel competency, including ensuring that staff have appropriate education and required state licenses
- Evaluation of performance on proficiency testing for all tests the laboratory performs for which PT is required by CLIA
- Quality assessment of general laboratory systems

Pre-analytic systems include requirements for:

- Test requisitions (e.g., patient name, date of birth, test to be performed, date the specimen was collected)
- Specimen submission, handling, and referral (e.g., labeling, storage, transport)

Analytic systems include requirements for:

- Procedure manuals
- Test systems, equipment, instruments, **reagent**s, materials, and supplies
- Establishment and verification of performance specifications
- Maintenance and function checks
- Calibration and calibration verification procedures
- Control procedures
- Specific standards based on the type of **nonwaived** test (e.g., bacteriology or virology)
- Comparison of test results
- Corrective actions
- Test records
- Analytic systems quality assessment

Post-analytic systems include requirements for regularly assessing and mitigating problems in the post-analytic systems, including standards for test reports and a general post-analytic systems quality assessment. Test reports must include the following (among other requirements):

- Patient identifiers
- Name and address of the laboratory where the test was performed
- Test report date
- Test performed
- Specimen source (and quality if the specimen did not meet laboratory requirements)
- Test results and units of measurement or interpretation, if applicable
- Laboratories must immediately alert the ordering provider if the test result is a "panic value" that indicates an imminently life-threatening condition

4.5 High Complexity Standards

Under **CLIA**, all LDTs are classified as high complexity tests. As a result, labs developing LDTs must meet all applicable CLIA requirements for high complexity testing before being used on patients. (CLIA quality standards described in 42 CFR Part 493, Subparts H, J, K and M). For instance, proficiency testing is required for all moderate to high complexity tests under CLIA.

As high complexity tests, LDTs must adhere to stringent CLIA requirements prior to being used on patients.

CLIA regulatory requirements for the laboratory and its operations—including staffing, quality control processes, and more—differ based on the complexity of the test. Specifically, high complexity tests (such as LDTs) must be performed in high complexity CLIA laboratories; such laboratories are run by a laboratory director who is required to have additional training and experience, compared to the director of a moderate complexity lab.

The following sections in 42CFR pertain specifically to high complexity laboratories:

- Conditions of laboratories performing high complexity testing
- Standards for laboratory director qualifications and responsibilities
- Standards for technical supervisor qualifications and responsibilities
- Standards, conditions, and qualifications for clinical consults
- General standards, conditions, qualifications, and responsibilities for the supervisor (incl. specific qualification based on the types of tests performed in the laboratory)
- Standards, conditions, and qualifications for laboratory personnel
- Standards and responsibilities for testing personnel

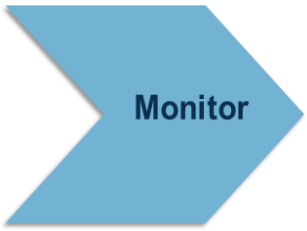
The high complexity tests procedure manual must be approved, signed, and dated by the lab director prior to use and when changes to procedures are made. The procedure manual must always be followed by all lab personnel.

A standard procedure manual includes standard operating procedures on, e.g., patient-sample identification and sample custody. While CLIA provides flexibility in establishing a system that works best for the lab, a procedure manual must be established per 42 CFR 493.1251 (Standard: Procedure manual). The procedure manual must be documented in writing and cover all tests, assays, and examinations performed by the lab.

CLIA regulations require that the procedure manual include information such as:

- Requirements for patient preparation; specimen collection, labeling, storage, preservation, transportation, processing, and referral; and criteria for accepting/rejecting patient samples
- Microscopic examination, including the detection of inadequately prepared slides

- Step-by-step performance of the procedure, including test calculations and interpretation of results
- Preparation of slides, solutions, calibrators, controls, reagents, stains, and other materials used in testing
- Calibration and calibration verification procedures.
- The **reportable range** for test results for the test system
- Control procedures
- Corrective action to take when calibration or control results fail to meet the laboratory's criteria for acceptability
- Limitations in the test methodology, including interfering substances
- **Reference interval**s (normal values)
- Imminently life-threatening test results, or panic or alert values
- Pertinent literature references
- The laboratory's system for entering results in the patient record and reporting patient results including, when appropriate, the protocol for reporting imminently life-threatening results, or panic, or alert values
- Description of the course of action to take if a test system becomes inoperable



5 Clinical Use

For providers to use the test on patients in a clinical setting, the test must be orderable via one of the following:

- **Electronic Medical Record (EMR)**
- Lab test requisition form
- Online portal

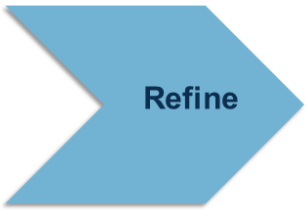
LDT test results must be returned to the ordering provider in a manner that is **HIPAA** compliant. This means that protected or personal health information such as test results, medical history, insurance information, and other healthcare information, must be shared and transmitted in a safe manner. All test results must be returned to the ordering provider by either:

- EMR
- FAX
- Online portal

Although LDTs might be based on (novel) research findings, they are clinical (not research) tests and are completely designed, manufactured, and used within a single, clinical laboratory. Once an LDT is used by healthcare providers on patients and processed in the innovator's clinical lab an LDT is considered "on the market." A good example is an antigen test used for the detection of the virus that causes COVID-19.

Resources:

- GOV: Interoperability and Patient Access, Final Rule
- Article: Weaving together Access, HIPAA & Electronic Health Information (EHI) Exchange



6 Test Capacity Expansion

An LDT can only be manufactured within the laboratory that designed it so the ability to scale production is limited by the testing capacity of that lab. There are many options for expanding the testing capacity of a laboratory, but careful consideration of **CLIA** requirements is critical to ensure the test stays within FDA's definition of an LDT.

If the manufacturing lab is a research laboratory, then substantial changes to the personnel and procedures could be required to meet CLIA requirements and offer the LDT to patients. Those requirements can be found in the brochures listed on the CMS.gov website and are described further below.

An LDT is considered "manufactured at market scale" when it becomes an orderable test for healthcare providers. Market scale can also be achieved through other measures; for instance, by expanding the test panel scope. Unlike **FDA**-cleared/approved **IVD**s, LDTs are not subject to design freezes, and you can add **analyte**s to your existing LDT panel at any time. A good example of this approach is adding the detection of influenza A and B to a testing panel created to detect the SARS CoV-2 virus. When a change to the test is made, CLIA requires that the laboratory validate the test and document the results of the validation prior to offering the test to patients.

If you add analytes to your LDT panel, you must revalidate the test with the new analytes added and document it in your records.

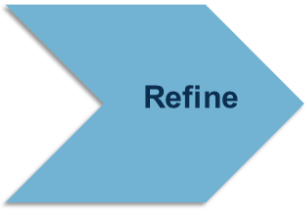
Market scale can also be achieved by offering the test to more patients through efficient standard operating procedures and ordering processes.

A laboratory operates as a **reference laboratory** when it receives a specimen from another laboratory and then performs one or more tests on the samples received. Although LDTs are not developed for the purpose of marketing or using them outside of the original facility, some LDTs are ordered by providers from other institutions. In this instance, the original lab acts as the reference lab. However, LDTs cannot be offered to and/or operated by any other, third-party lab. Note that if the test is sold, in whole or in part, to other laboratories, it is required to obtain FDA premarket approval or clearance.

Importantly, CLIA is a program that is operated jointly by the federal government and individual states. Thus, while CLIA sets minimum requirements laboratories in all states must meet, some states have additional requirements. Further, some of CLIA's requirements concern the licenses held by laboratory

personnel, and the types of licenses available and the training needed to obtain them varies from state to state.

It is important that if an LDT is used by providers from other states that the specific state lab and lab testing licensure requirements are met by the original lab (in addition to CLIA requirements.) The test can only be processed, run, and evaluated in the original lab.



7 Direct-to-Consumer (DTC) Testing

FDA defines DTC tests as devices that are marketed directly to individuals without the involvement or guidance of a healthcare provider. FDA generally does *not* exercise enforcement discretion for DTC tests regardless of whether they meet the definition of an LDT; most LDTs are not marketed directly to consumers.

Some DTC tests are reviewed by FDA while others are not. In general, DTC tests for non-medical, general wellness, or low-risk medical purposes are not reviewed by FDA. However, DTCs that have an impact on medical care and clinical decision making typically are reviewed by FDA.

DTC tests for moderate- to high-risk medical purposes, which may have a higher impact on medical care, are generally reviewed by FDA to determine the validity of test claims.

When reviewing tests, FDA assesses the tests' **analytical validity** and **clinical validity**, and the company's claims about the test's performance. FDA also looks at whether the test offers accurate descriptive information that can be easily understood by a consumer without the involvement of a healthcare provider. This is done by reviewing the language used to instruct users on collecting the sample and interpreting the test result report.

In addition to federal guidelines, there are state-specific guidelines to be considered before marketing directly to consumers. While some states are considered "Direct Access Testing" states, such as Virginia, and allow DTC marketing, certain other states, such as Maryland and New York, prohibit the marketing or advertising of laboratory testing *directly to patients*. Detailed review of such restrictions should be conducted for each state. Laboratories serving patients from other states (i.e., samples are collected from patients that reside outside the state where the lab is located) may have to also obtain certain state-specific lab permits from the state's Health Department. These requirements also vary by state.

For additional information regarding DTC testing, please contact the SEED Innovator Support Team.

Resources:
FDA: Direct-to-Consumer Tests

FDA: Collaborative Review of Scientific Evidence to Support Associations Between Genetic Information and Specific Medications
FDA: FDA Authorizes First DTC Test for Detecting Genetic Variants That May Be Associated with Medication Metabolism
FDA: FDA Authorizes DTC Test That Reports Three Mutations in the BRCA Breast Cancer Genes

8 Appendix: Comparing Regulation of *In Vitro* Diagnostics and LDTs

	***In Vitro* Diagnostic Devices (IVDs)**	**Laboratory Developed Tests (LDTs)**
Lead Agency	**FDA** (Amended Medical Device Amendments of 1976)	**CMS** Public Health Services Act, amended by CLIA
Applicable Regulations	**21 CFR 800 Medical Devices** 21 CFR 801 and 809 *Labeling* 21 CFR 803 *Reporting* 21 CFR 807 *Establishment Registration & Device Listing* 21 CFR 809 *In Vitro Diagnostic Products for Human Use* 21 CFR 810 *Recall Authority* 21 CFR 814 *Premarket Approval* 21 CFR 820 *Manufacturing and Quality System Regulation (GMP)*	**42 CFR 493 Laboratory Requirements** 42 CFR 493.1 *General Provisions* 42 CFR 493.1253(b)(2) *Establishment of performance specifications* *42 CFR 493.17(c)(4) and 493.25 Test Categorization and Laboratories performing tests of high complexity.* 42 CFR 493.35-493.63 *Certificate of Waiver; Registration Certificate; Certificate of Compliance; Certificate of Accreditation* 42 CFR 493.551 *Accreditation by a Private, Nonprofit Accreditation Organization or Exemption Under an Approved State Laboratory Program* 42 CFR 493.602 *General Administration* 42 CFR 493.801 *Participation in Proficiency Testing for Laboratories Performing Nonwaived Testing* 42 CFR 493.1100 *Facility Administration for Nonwaived Testing* 42 CFR 493.1200 *Quality System for Nonwaived Testing* 42 CFR 493.1351 *Personnel for Nonwaived Testing* 42 CFR 493.1771 *Inspection*
Laboratories Performing the Test	Sold to, and performed by, multiple laboratories, in clinical use for diagnostic testing; includes licensing	Performed by the single laboratory in which the test was developed, for clinical diagnostic testing
Premarket Clearance or Approval	IVDs must be cleared 510(k) or approved (PMA) before they are sold; must be listed as a medical device with FDA	*** No FDA premarket regulatory approval process for LDTs. LDT samples may only be accepted by a clinical laboratory with a CMS CLIA Certification (or equivalent); test validation information is reviewed during CMS CLIA lab licensure (re)inspection (42 CFR 493.1771)*
Adverse Events	Medical Device Reporting regulation (21 CFR Part 803) – including device related adverse events and product problems/malfunctions	*** No adverse event reporting process for LDTs. Submit a corrected test report consistent with (42 CFR 493)*

Establishment Registration	IVD manufacturers must register their establishment with FDA (electronically) and pay the corresponding fee	*** LDTs are not required to register and list with FDA but laboratories performing LDTs must have a current CMS CLIA Certification (or equivalent) and other state-specific licenses and paid the corresponding fee(s)*
Assessment of Clinical Validity	Clinical validity assessed as part of premarket clearance or approval	*** Under CLIA the clinical validity of LDTs is NOT assessed*
CLIA Complexity	Set for device by FDA based on level of complexity (waived, moderate, or high complexity)	*** All LDTs are considered high complexity tests; LDTs must only be used by laboratories that meet the requirements for high complexity testing under CLIA as described in 42 CFR 493.17(c)(4) and 493.25.*
Direct-to-Consumer Testing	21 CFR 866.5940 Carrier Screening Tests 21 CFR 866.5950 Genetic Health Risk (GHR) Tests 21 CFR 862.3364 Pharmacogenetics Tests 21 CFR 866.6090 Cancer Predisposition Tests	*** FDA generally does not exercise enforcement discretion for DTC tests regardless of whether they meet the definition of an LDT; most LDTs are not marketed direct to consumers; exceptions to FDA enforcement are covered in the guide below.*
Other	Special controls, such as specific labeling requirements, mandatory performance standards, or specific post-market surveillance activities laid out by FDA as part of approval conditions. 21 CFR 812 allows an investigational device to be used in a clinical study.	*** No special controls for LDTs*

Updated October 2023