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Clinical Laboratory Improvement Amendments (CLIA) and Regulatory Oversight

How is "clinical laboratory" defined?

The Code of Federal Regulations in the United States defines a laboratory as follows:

> "...a facility for the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings. These examinations also include procedures to determine, measure, or otherwise describe the presence or absence of various substances or organisms in the body. Facilities only collecting or preparing specimens (or both) or only serving as a mailing service and not performing testing are not considered laboratories." (42 CFR §493.2) (1)

Laboratories that operate as defined above are subject to regulation by the Clinical Laboratory Improvement Amendments (CLIA) and are often referred to as clinical laboratories. The term clinical laboratories will be used throughout this book to refer to laboratories regulated by CLIA.

There are some key aspects that help identify a clinical laboratory based on the definition above:

What is occurring in the laboratory? Laboratories must be involved in testing. If a location is handling specimens for other purposes but is not performing any testing, they are not considered a clinical laboratory.

What is being tested? The laboratory must examine human specimens, which refers to any materials that are obtained from humans. These include but are not limited to blood, body fluids and secretions, tissues, urine, stool, hair and nails, and swabs from various body sites. Human samples collected postmortem during an autopsy may also be tested in clinical laboratories (2).

What is the purpose of testing? The purpose of testing in the laboratory must be for patient management. This can include testing to assist in diagnosis, monitor disease progress, track treatment impact, engage in preventative care, or assess potential organ donors (3).

Other laboratories may perform testing on human samples, but not for the purposes of health assessment and patient management. These are not considered clinical laboratories and they are not subject to CLIA requirements. Examples of such laboratories include research laboratories, forensic laboratories, and laboratories certified by the Substance Abuse and Mental Health Services Administration

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(SAMSHA) that perform only drug testing (other testing performed in SAMSHA certified laboratories may require a CLIA certificate) (4).

What is CLIA?

CLIA stands for Clinical Laboratory Improvement Amendments. When someone mentions "CLIA" they may be talking about either CLIA law or CLIA regulations. CLIA law refers to the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88) (Public Law 100-578), which were amendments to the Clinical Laboratories Improvement Act of 1967 (CLIA'67) and were signed into law in 1988. CLIA regulations, on the other hand, are requirements codified in the Code of Federal Regulations (42 CFR §493 *Laboratory Requirements*). CLIA regulations were issued by the Centers for Medicare and Medicaid Services (CMS) in 1992 in order to enact CLIA'88. From 1992 to 1994, CLIA regulations were phased in. Amendments to these regulations have occurred periodically since then. For further information on CLIA regulations see section ***What is the Code of Federal Regulations (CFR)?*** The section here will discuss CLIA law.

The Clinical Laboratories Improvement Act of 1967 (Public Law 90-174)

In 1967, a new section (Sec. 353) was added to the Public Health Service Act (5). Titled *Licensing—Biological Products and Clinical Laboratories*, the purpose of this addition was briefly noted as "to improve the performance of clinical laboratories." Also known as The Clinical Laboratories Improvement Act of 1967 (CLIA'67), this brief section represented the establishment of quality standards for clinical laboratories in the United States.

CLIA'67 required interstate laboratories performing testing on human samples for the purposes of diagnosis, prevention, treatment, or assessment of a disease or condition to obtain a license to operate. In order to obtain and maintain a license, laboratories needed to demonstrate adherence to certain standards meant to improve clinical laboratory quality and ultimately ensure patient safety. Specifically, the standards were meant to ensure: 1) maintenance of a quality control program, 2) maintenance of records, equipment, and facilities, 3) qualifications of the laboratory's director(s) and other personnel, and 4) participation in a proficiency testing program.

CLIA'67 had a relatively limited reach, however. It only applied to laboratories that took part in "interstate commerce" i.e., only laboratories that did business across state lines. Laboratories accredited by any accrediting agency with requirements equal to or more stringent than those found in CLIA'67 were exempt from the licensing requirement, as were smaller laboratories and labs whose activities remained within one state. CLIA'88 would widen that reach.

The Clinical Laboratory Improvement Amendments of 1988 (Public Law 100-578)

In late 1987, two articles were published in *The Wall Street Journal* by journalist Walt Bogdanich detailing false negative Papanicolaou (Pap) smear results that led to missed diagnoses in cervical cancer screening (6, 7). Bogdanich's articles suggested that the inaccurate Pap smear results were due to overwork, lack of quality control, and lack of appropriate education for testing personnel (6-8). In response to the resulting public upset and in order to strengthen and improve existing laws governing clinical laboratories, Congress passed the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88) (8).

CLIA'88 outlined several amendments to Public Health Service Act section 353. Important among these changes was the establishment of minimum standards for all clinical laboratories in the U.S., not just those

involved in interstate commerce (9). Also included in CLIA'88 was the requirement for development of standards for: laboratory personnel qualifications, quality control (QC) and quality assurance (QA) procedures, and proficiency testing requirements. CLIA'88 also introduced waived and nonwaived test categorization.

Two amendments to CLIA'88 were later implemented, one in 1997 to update the criteria for waived testing and one in 2012 related to proficiency testing referral (10, 11). Despite these recent amendments, CLIA law is still referred to as CLIA'88.

What is the Code of Federal Regulations (CFR)?

The Code of Federal Regulations (CFR) is the codification of regulations set forth by federal departments and agencies in the United States. The official CFR is reviewed and published annually by the Office of the Federal Register. An unofficial "point in time" version can be found online and is known as the Electronic Code of Federal Regulations (e-CFR) (https://www.ecfr.gov/).

The CFR provides regulations for a wide range of industries and sectors, including clinical laboratories. Specifically, Title 42 Part 493 (42 CFR §493), titled "Laboratory Requirements," details the regulations all clinical laboratories must follow in order to acquire and maintain certification to perform human specimen testing under CLIA '88 (1). In other words, the CFR contains the federal requirements a clinical laboratory must comply with in order to legally test human samples for health care purposes. 42 CFR §493 provides regulations for all clinical laboratories, including those performing microbiology and serology testing on human specimens. As with CLIA law, the purpose of 42 CFR §493 is to provide quality standards that clinical laboratories must meet, with a mind toward ensuring quality testing and patient safety.

42 CFR §493 provides regulations on several topics ranging from how clinical laboratories acquire and maintain certification, to personnel qualifications, to details on how to maintain a quality system for every type of system. Several topics within 42 CFR §493 will be covered in this book, however readers are advised to read through 42 CFR §493 for official information (https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493). Though the CFR is an excellent resource for clinical laboratory administrators, it can sometimes be unclear. To aid laboratories in interpreting how to fulfill various requirements, the Centers for Medicare and Medicaid Services (CMS) publishes interpretive guidelines that accompany 42 CFR §493 (12).

What roles do the Centers for Medicare and Medicaid Services (CMS), the Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA) play in regulating clinical laboratories?

Three federal agencies are responsible for administering CLIA in the United States: the Centers for Medicare and Medicaid Services (CMS), the Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA). Each agency has distinct but complementary roles in administering CLIA and providing support and oversight for clinical laboratories (4, 13-15).

CMS regulates clinical laboratory testing in the United States under CLIA. Specifically, CMS does the following:

- Develops and publishes CLIA regulations
- Issues CLIA certificates to clinical laboratories
- Approves accreditation agencies that perform inspections
- Performs inspections
- Approves state exemptions for state programs deemed equivalent to CLIA (currently only Washington state and New York

state are exempt from CLIA program requirements) (16)
- Enforces regulatory compliance

The CDC supports the administration of CLIA through its Clinical Laboratory Improvement Advisory Committee (CLIAC) and provides several services that aid clinical laboratories in improving quality. The CDC supports clinical laboratories by:

- Advising the U.S. Department of Health and Human Services (HHS) on scientific and technical issues pertaining to clinical laboratories, with a focus on improving quality and practices. This is achieved through the CDC's CLIAC. CLIAC also provides guidance on revisions to CLIA standards (17). Committee members represent all disciplines of the clinical laboratory and are professionals working in clinical, academic, and industry spaces. CLIAC meetings are open to the public and can be viewed virtually.
- Publishing guidelines and recommendations for testing and treatment of diseases, including infectious diseases
- Providing online training courses and videos for laboratory professionals. Training activities can be found here: https://www.cdc.gov/lab-training/php/onelab/

The FDA is responsible for:

- Reviewing applications for authorization of *in vitro* diagnostic (IVD) devices and subsequently clearing, approving, or granting manufacturers the ability to market IVDs
- Designating IVDs into one of three CLIA categorizations. In order of least to most complex, tests are categorized as either waived tests, moderate-complexity tests, or high-complexity tests.

The FDA also has authority to regulate laboratory developed tests (LDTs), and, until recently, they have chosen to exercise "enforcement discretion" such that they did not require premarket notification or approval for these assays. However, the FDA has announced they will be phasing out this enforcement discretion in conjunction with their issuance of the final rule. The final rule amends FDA regulations to state that IVDs that are developed by clinical laboratories are now subject to the Federal Food, Drug, and Cosmetic (FD&C) Act (18). See sections ***What is a laboratory developed test (LDT)?*** and ***What does the FDA final rule mean for my laboratory?*** for additional information of the FDA's role in overseeing LDTs.

What is an FDA-cleared or FDA-approved test?

Tests that are performed on human samples (e.g., blood, body fluids or secretions, tissue) for the purpose of screening, diagnosis, or monitoring of diseases or other conditions are known as *in vitro* diagnostic (IVD) products. Before a manufacturer introduces an IVD to the market, they are required to notify the FDA of their intent to put that device on the market. To do this, manufacturers must submit premarket notification (510(k))[1] applications, premarket approval (PMA) applications, or De Novo classification requests to the FDA, who will then review applications to ensure that the device is both safe and effective before its introduction to the market (19).

Class I or II[2] IVDs being introduced to the market for the first time and that are considered "substantially equivalent" to another device already on the market (also known as a predicate device) are required to go through the

1 The term "510(k)" comes from section 510(k) of the Federal Food, Drug, and Cosmetic Act, which states the requirement for premarket notification submissions.

2 Class I, II, and III are classifications assigned to medical devices by the FDA based on the level of control needed to ensure the safety and efficacy of that particular device. Class I devices are considered the lowest risk with the lowest level of control necessary, class II devices are moderate risk and require additional controls, and class III devices are the highest risk and require more rigorous review. Diagnostic devices for the clinical microbiology laboratory may fall into any of these classes.

510(k) premarket notification review process. If the 510(k) review process is successful, these devices are cleared by the FDA (FDA cleared) and may be legally placed on the market (20, 21).

IVDs that are classified as class III devices—which are considered the most high-risk devices and therefore require the most stringent regulatory control—and are introduced to the market for the first time are required to go through the premarket approval (PMA) process. If the PMA review process is successful, these devices are approved by the FDA (FDA approved) and may be legally placed on the market (22, 23).

De Novo classification requests may be submitted for IVDs being introduced to the market for the first time and that meet the standards for low- or moderate-risk devices (likely to be classified as class I or II), but that do not have a substantially equivalent (predicate) device already on the market[3] . If the De Novo review process is successful, the FDA grants the manufacturer the right to legally place the device on the market. The device can then be used as a predicate device for future 510(k) submissions.

As a point on terminology, the various submissions result in scenarios where the FDA may **clear** (510(k)), **approve** (PMA), or **grant** (De Novo) a manufacturer's ability to legally market a device.

What is a laboratory developed test (LDT)?

The FDA defines a laboratory developed test (LDT) as "...an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory." (24). In other words, if a clinical laboratory develops their own test for use in patient testing, it is considered an LDT. Additionally, if a clinical laboratory makes any modifications to an FDA-cleared or FDA-approved test, the modified test is also considered an LDT. The FDA considers a single laboratory to be a facility with a single CLIA certificate[4]. Therefore, if an LDT is being used under multiple CLIA certificates, it is not considered an LDT under the FDA definition and is out of compliance. Similarly, if a test is developed or manufactured partially or completely outside of a single laboratory, it is not considered an LDT and is out of compliance. Components of LDTs should include general purpose reagents (GPRs), analyte specific reagents (ASRs), or in-house materials (25). ASRs and GPRs manufactured outside of the laboratory do not violate the FDAs requirement for a test to be manufactured completely within a single laboratory (26). LDTs may only be used in laboratories that meet the CLIA requirements for high-complexity testing (see 42 CFR §493.17(c)(4) and 42 CFR §493.25) (1).

The FDA has authority to regulate LDTs, and, until recently, they have chosen to exercise "enforcement discretion" such that they did not require premarket notification or approval for these assays. Throughout the past decades, the FDA has written several draft guidances and documents regarding the regulation of LDTs. In May 2024, the FDA announced they were amending their regulations with regard to LDT oversight, such that LDTs are now subject to certain FDA regulations, including premarket notification or approval (with some exceptions) (18). See ***What does the FDA final rule mean for my laboratory?*** below for additional information on this announcement and how it affects clinical laboratories in the United States.

3 Historically, all devices submitted for premarket notification (510(k)) that did not have a predicate device were automatically classified as class III and required to go through PMA review, regardless of their level of risk and the controls necessary to ensure safety and effectiveness. The De Novo pathway was created to allow for a more accurate and efficient pathway to market for low- (class I) and moderate-risk (class II) medical devices. Class III devices still must go through the PMA review process.

4 See Chapter 2 ***What are the types of CLIA certificates?***

What does the FDA final rule mean for my laboratory?

In May 2024, the FDA published details of the previously announced final rule regarding their oversight of LDTs (18). This rule updated FDA regulations such that the definition of IVDs under the Federal FD&C Act includes IVDs that are "manufactured" by laboratories[5]. In other words, it unequivocally gives the FDA oversight of the regulation of LDTs. In addition to this update, the FDA also announced they would be phasing out the "enforcement discretion" they have previously implemented for LDTs, meaning that in most instances clinical laboratories that develop and use LDTs must now comply with several regulations that are applicable to IVD manufacturers (18). A high-level overview of the applicable FDA requirements, the expected implementation stages and compliance start dates, and the affected LDT types will be discussed in this section. As a reminder, only clinical laboratories that meet the CLIA requirements for high-complexity testing may develop and use LDTs.

FDA Requirements

The FD&C Act is a set of laws that grant the FDA the authority to regulate the production, sale, and distribution of medical devices[6] (as well as other products) in the United States. These laws are codified within Title 21 of the CFR. The regulations specifically governing medical devices are found in Title 21 Parts 800–898. Under the amended regulations, clinical laboratories that produce and "market"[7] LDTs must now comply with a subset of these requirements, specifically the following (18):

- Medical Device Reporting (MDR) (21 CFR Part 803)
- Correction and Removal Reporting (21 CFR Part 806)
- Registration and Listing (21 CFR Part 807)
- Labeling (21 CFR §809.10)
- Investigational Use (21 CFR Part 812)
- Premarket Review Submission for High-Risk IVDs (21 CFR Part 814)
  - High-risk IVDs are reviewed through the PMA process
- Premarket Review Submission for Low- and Moderate-Risk IVDs (21 CFR Part 807 Subpart E for 510(k) submissions; and 21 CFR Part 860 Subpart D for De Novo submissions)[8]
  - Low- and moderate-risk IVDs are reviewed through the premarket notification (510(k)) or De Novo processes
- Quality System Regulations
  - Only a subset of the quality system regulations (found in Part 820) is applicable to clinical laboratories. Specifically, clinical laboratories must comply with the following requirements:
    - Design Controls (21 CFR §820.30)
    - Purchasing Controls (21 CFR §820.50)
    - Acceptance Activities (21 CFR Part 820 Subpart H)
    - Corrective and Preventive Actions (21 CFR §820.100)

5 The updated wording for the definition of IVDs can be found in the eCFR under 21 CFR §809.3(a), which now in part reads "These products are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act, *including when the manufacturer of these products is a laboratory*." (emphasis identifies the updated wording and was added by the author).

6 This includes IVDs.

7 The FDA is using the terms "market" or "marketed" to describe the development and use of LDTs by clinical laboratories.

8 IVDs that are intended for use in donor screening are licensed for marketing (instead of cleared, approved, or granted) by the FDA through the Biologics License Application (BLA) process, which is detailed in 21 CFR Part 601. Clinical laboratories that produce and use LDTs for donor screening may be required to comply with this and other regulations and are encouraged to reach out to the FDA for additional information.

- Records (21 CFR §820.180-186)
- Complaint Files (21 CFR §820.198)

These requirements are substantial, and most are significantly different than the requirements clinical laboratories are familiar with. It will take time to implement processes for meeting these requirements within clinical laboratories. Laboratories that currently develop and use LDTs, or intend to do so in the future, should therefore familiarize themselves with these requirements as soon as possible and reach out to the FDA with questions.

Implementation Stages and Compliance Start Dates

The FDA is implementing a phaseout policy wherein they are phasing out the general enforcement discretion they previously applied. This phaseout policy is being undertaken in five stages over four years. For each stage, there is an accompanying date that identifies when clinical laboratories are expected to be compliant with the regulations in each stage. This date is designated as the compliance start date in this book. Each stage is described below, including the compliance start date and the regulations included in that stage (18). This information is also shown in **Table 1–1**.

- Stage 1: Clinical laboratories that produce IVDs must comply with the medical device reporting, correction and removal reporting, and complaint files requirements. Compliance with these requirements is expected starting May 6, 2025.
- Stage 2: Clinical laboratories that produce IVDs must comply with the registration and listing, labeling, and investigational use requirements. Compliance with these requirements is expected starting May 6, 2026.
- Stage 3: Clinical laboratories that produce IVDs must comply with the remaining quality system requirements not already addressed in stage 1. This includes the design controls, purchasing controls, acceptance activities, corrective and preventive actions, and records requirements. Compliance with these requirements is expected starting May 6, 2027.
- Stage 4: Clinical laboratories that produce IVDs must comply with the premarket review requirements for high-risk IVDs by submitting a PMA. Compliance with this requirement is expected starting November 6, 2027.
- Stage 5: Clinical laboratories that produce IVDs must comply with the premarket review requirements for low- or moderate-risk IVDs by submitting a premarket notification (510(k)) or a De Novo request. Compliance with these requirements is expected starting May 6, 2028.

LDT Categories

There are several categories into which the FDA has organized LDTs, each of which is described here (18). It is important for laboratory personnel to have a good understanding of what types of LDTs are included in each category since the above-mentioned requirements will be applicable to some but not all categories (see the discussion on targeted enforcement discretion below).

- 1976-type LDTs: This category includes tests that have certain characteristics in common with LDTs that were offered in 1976, when the original enforcement discretion came into effect. These characteristics include (18):
  - Techniques are performed manually (with no automation) by laboratory personnel with specialized expertise
  - Components used for the test are legally marketed for clinical use
  - The test is developed and used within a single clinical laboratory that meets the CLIA requirements for high-complexity testing
- Human leukocyte antigen (HLA) LDTs for transplantation: This category refers to HLA tests that are considered LDTs (i.e., developed

Table 1-1 Intended FDA Final Rule Compliance Requirements by LDT Assay Type. This table lists each of the FDA compliance requirements for LDTs manufactured in clinical laboratories, as well as the expected stage and compliance start dates for each requirement, and where in Title 21 of the CFR each requirement is detailed. For each LDT category, the applicable requirements are also identified. Note that for 1976-type LDTs, HLA LDTs for transplantation, forensic tests, and DoD and VHA LDTs, the FDA intends to continue applying enforcement discretion, such that compliance is not expected for any of the listed requirements. Clinical laboratories must comply with the requirements for the remaining LDT categories as applicable. Applicable requirements for each category are indicated as "Yes" in the table. For information on each type of LDT category, see section ***What does the FDA final rule mean for my laboratory?*** main text. LDTs that must comply with premarket submission requirements should submit an application for only one of the pathways (PMA, 510(k), or De Novo) depending on the device's expected risk level and whether there is a predicate device.

FDA Requirements for Laboratory Developed Test Compliance													
Stage	**Stage 1**			**Stage 2**			**Stage 3**					**Stage 4**	**Stage 5**
Compliance Start Date	**May 6, 2025**			**May 6, 2026**			**May 6, 2027**					**Nov 6, 2027**	**May 6, 2028**
							Quality System						
Requirement	**Medical Device Reporting**	**Correction and Removal Reporting**	**Quality System: Complaint files**	**Registration and Listing**	**Labeling**	**Investigational Use**	**Design Controls**	**Purchasing Controls**	**Acceptance Activities**	**Corrective & Preventive Actions**	**Records**	**Premarket Review Submission (PMA)**	**Premarket Review Submission (510(k), De Novo)**
21 CFR Section	Part 803	Part 806	§820.198	Part 807	§809.10	Part 812	§820.30	§820.50	Part 820, Subpart H	§820.100	§820.180-186	Part 814	Part 807, Subpart E (510(k)) Or Part 860 Subpart D (De Novo)
LDT Categories & Applicable Requirements													
1976-Type LDTs	The FDA intends to exercise enforcement discretion for these LDTs. Laboratories are not required to comply with any of the above requirements for these LDT assays.												
HLA for Transplant	The FDA intends to exercise enforcement discretion for these LDTs. Laboratories are not required to comply with any of the above requirements for these LDT assays.												

Forensic Tests	The FDA intends to exercise enforcement discretion for these LDTs. Laboratories are not required to comply with any of the above requirements for these LDT assays.												
DoD and VHA	The FDA intends to exercise enforcement discretion for these LDTs. Laboratories are not required to comply with any of the above requirements for these LDT assays.												
NYS CLEP-Approved	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		
Rare RBC Antigens	Yes	Yes	Yes	Yes	Yes	Yes					Yes		
Unmet Needs	Yes	Yes	Yes	Yes	Yes	Yes					Yes		
Currently Marketed	Yes	Yes	Yes	Yes	Yes	Yes					Yes		
Minor Modifications (Marketed LDT)[a]	Yes	Yes	Yes	Yes	Yes	Yes					Yes		
Significant Modifications (Marketed LDT)[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Minor Modifications (510(k) or De Novo)[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		
Significant Modifications (510(k) or De Novo)[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other (Including New LDTs)[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[a] These modifications refer to changes made to currently marketed LDTs. See section ***What does the FDA final rule mean for my laboratory?*** main text for information on significant versus minor modifications.

[b] These modifications refer to changes made to another manufacturer's 510(k)-cleared or De Novo authorized test. See section ***What does the FDA final rule mean for my laboratory?*** main text for information on significant versus minor modifications.

[c] New LDTs are those that are introduced for use into a single laboratory eligible to perform high-complexity testing on or after the final rule issuance date of May 6, 2024.

and used within a single laboratory that meets the CLIA requirements for high-complexity testing), and that are used to perform HLA allele typing, HLA antibody screening and monitoring, and HLA crossmatch tests (real or virtual) in order to aid in organ, tissue, and/or stem cell transplantation (18).

- Forensic tests: These are tests that are used only for law enforcement purposes.
- Department of Defense (DoD) and Veterans Health Administration (VHA) LDTs: This category includes LDTs that are developed and used within DoD or VHA facilities, and that are only used for testing patients that are undergoing testing or treatment within DoD or VHA facilities.
- New York State Clinical Laboratory Evaluation Plan (NYS CLEP)-approved LDTs[9]: This category refers to LDTs that have been granted either full approval or conditional approval under NYS CLEP. Note that if an LDT under conditional approval does not receive full approval and the conditional approval is withdrawn, the LDT no longer falls into this category and will be subject to applicable requirements for the LDT category it falls under.
- Nonmolecular antisera LDTs for rare red blood cell (RBC) antigens: This category includes tests that are developed and performed within blood establishments (e.g., transfusion services, immunohematology laboratories). There must be no alternative IVD available for achieving a compatible blood transfusion in order for LDTs to fall into this category. The FDA specifically states that this category does not include molecular tests for genotyping RBC antigens.
- LDTs for unmet needs: This category refers to tests for which no FDA-authorized alternative exists (or for which authorized alternatives do not "reflect the latest advances in science") (18). This includes the following scenarios:
  - For rare diseases or conditions
  - An authorized IVD exists but is not indicated for use for the patient, or doesn't meet the patient's needs
  - An authorized IVD exists but is not available for use for the patient (e.g., the sample is unable to be sent to the testing laboratory)

  There are several additional caveats for this category that laboratory personnel should be aware of, since these criteria may make it challenging for LDTs to qualify for this category—even if they are intended for an unmet need[10] (18).
  - These LDTs must be validated by the clinical laboratory that developed and intends to use them.[11]
  - These LDTs must be used only within a laboratory integrated into a health care system.

9 For laboratories that produce LDTs to test patient samples originating in New York state (whether the laboratory is in New York state or out of state), NYS CLEP requires these LDTs to undergo review. This may be achieved through either CLEP review (these LDTs will then fall under the NYS CLEP-approved category) or FDA review (these LDTs would likely be subject to requirements for the "other LDTs" category). Laboratories are encouraged to reach out to NYS CLEP and the FDA with questions.

10 This category is unlikely to be viable in most settings, including reference laboratories and most routine clinical laboratories. Not all reference laboratories are integrated into a health care system; reference laboratories by definition serve patients from external institutions; and the ordering provider is unlikely to be employed by the same system that houses the reference laboratory (even if the laboratory is integrated into a health care system). Since most routine clinical laboratories will have insufficient test volume to make an unmet needs LDT worthwhile, this category is also unlikely to be viable in these laboratories. This category could be useful for laboratories within health care systems that primarily serve patients from specific populations where unusual illnesses or infections are common (e.g., a clinical microbiology laboratory within a cancer center or transplant center).

11 See Part II **Going Live: Verification and Validation of Test Systems** for additional information on performing validation studies.

  - The laboratory director of the integrated laboratory must be on staff within the same health care system as the laboratory and the ordering provider.
  - The test must be ordered by a provider that is on staff within the same health care system as the laboratory and the laboratory director.
  - These LDTs may only be used for patients being treated within the health care system housing the laboratory. This does NOT include patients at affiliated hospitals that have different corporate ownership than the laboratory.
  - Once an FDA-authorized IVD that meets the patient's needs is available, the LDT no longer falls into this category.
- Currently marketed LDTs: This category refers to LDTs that were developed and in use within a single laboratory that meets CLIA requirements for high-complexity testing prior to the date the final rule was issued (May 6, 2024). Any LDTs introduced for use on or after this date do not fall into this category. If modifications are made to a currently marketed LDT after the issuance date, the test may no longer fall into this category (see the description of modified currently marketed LDTs below).
- Modified currently marketed LDTs: This refers to LDTs that were developed and in use within a single laboratory that meets CLIA requirements for high-complexity testing prior to the date the final rule was issued (May 6, 2024) but where modifications were made to the test on or after the issuance date. Modifications may be considered minor, or significant. The FDA considers the following modifications to be significant (FDA examples are also provided) (18):
  - A change in the indications for use
  - A change in the method principle (e.g., critical reaction components)
  - Introduction of a significantly different technology (e.g., artificial intelligence, change from manual to automated processes, change from targeted to whole-genome sequencing)
  - A modification that results in an adverse change in assay performance specifications
  - A modification that results in an adverse change in safety specifications
- Modified FDA 510(k)-cleared or De Novo authorized LDTs: This category includes tests where a single laboratory that meets CLIA requirements for high-complexity testing makes modifications to a manufacturer's 510(k)-cleared or De Novo authorized test. It should be noted that this category does not include modifications to PMA approved tests. Modifications may be minor or significant. The FDA considers the modification to be significant in the following circumstances:
  - The modification leads to a significant change in the safety or effectiveness of the test
  - The modification results in a significant change to the assay intended use
- Other LDTs: This category includes LDTs that do not fall within any of the above categories. Examples include, but are not limited to:
  - LDTs that are developed and placed in use within a single laboratory that meets CLIA requirements for high-complexity testing on or after the final rule issuance date (May 6, 2024). These are called new LDTs in this book.
  - Modified PMA approved tests

Most routine clinical microbiology laboratories will likely only produce tests that fall under the currently marketed, modified (both modified LDT and modified 510(k)/De Novo), and other LDTs (i.e., new LDTs) categories. Laboratories that produce LDTs to test patient samples originating in New York state (whether the laboratory is in New York state or out of state) will likely also produce tests that fall under the NYS CLEP-approved category.

Targeted Enforcement Discretion

The previous FDA approach of enforcement discretion was considered general to all LDTs.

With the amendment to their regulations, the FDA is phasing out general enforcement discretion and replacing it with targeted enforcement discretion (18). What this means practically is that the above-mentioned FDA requirements will be differently applicable to different categories of LDTs. The applicable requirements for each LDT category are outlined in **Table 1–1**. Of note, there are four categories of LDTs where the FDA will continue to practice full enforcement discretion, meaning none of the requirements listed here will be applicable for those LDTs. These include: 1976-type LDTs, HLA LDTs for transplantation, forensic tests, and LDTs in DoD or VHA hospitals (18). Clinical laboratories developing and using tests that fall into the remaining LDT categories must comply with some or all of the requirements listed here[12] (**Table 1–1**).

Legal Challenges to the FDA Final Rule

Readers should be aware that while the FDA is moving forward with expecting compliance with the above-listed requirements, their authority to do so is being challenged**.** At the time of writing, there have been multiple lawsuits filed against the FDA with regard to the final rule, with complainants arguing that the FDA does not have the authority to regulate LDTs (27, 28). This, coupled with the overturning of the Chevron doctrine[13] by the United States Supreme Court in June 2024 has led some laboratory personnel to hope that the final rule will be struck down and that clinical laboratories and LDTs will no longer be subject to FDA oversight (29). However, at this time the status of the FDA final rule is that it is in effect. Therefore, clinical laboratories that currently use LDTs or that plan to develop LDTs in the future should begin moving toward adherence to applicable FDA requirements in time for the compliance start date of each stage. Up to date information on the FDA's expectations—including webinars, FDA contact information, and other resources to assist laboratory personnel—can be found on the FDA's website (https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests). Readers are also encouraged to check for current information on the status of related legal challenges and court decisions through professional organization websites[14], listservs[15], and national news outlets.

What is Emergency Use Authorization (EUA)?

During a declared emergency in the United States, the Secretary of the HHS may choose to authorize an unapproved drug, device (including *in vitro* diagnostic devices), or biological product for introduction into the market for use during an actual or potential emergency (30).

12 Laboratories developing and using LDTs to test patient samples originating in New York state (regardless of whether the laboratory is in New York state or out of state) should reach out to NYS CLEP for information on compliance requirements and routes to test approval (FDA review versus CLEP review).

13 The Chevron doctrine was a 1984 decision that established the precedence where courts defer to federal agencies' interpretations of vague or ambiguous laws. The overturning of this decision means that courts will be more likely to question or scrutinize rules driven by federal agency interpretations of vague laws, potentially including the final rule under discussion here.

14 The American Clinical Laboratory Association (ACLA) and the Association for Molecular Pathology (AMP) organizations were plaintiffs on separate lawsuits filed against the FDA. Their website newsrooms are therefore good resources for information on the filings and any updates.

15 The American Society for Microbiology (ASM) has two members-only clinical microbiology and public health listservs that provide updates on the final rule and associated lawsuits (among many other topics). These listservs are clinmicronet (meant only for laboratory directors) and divC (meant for all members of the clinical microbiology laboratory community). Information for ASM members on joining can be found here: https://asm.org/forms/listservs

Such authorizations are known as emergency use authorizations (EUAs). This includes drugs, devices, or biological products that are cleared, approved, or licensed but where the intended use in an emergency is for an unapproved use. In a circumstance where EUAs are determined to be necessary, the FDA is responsible for issuing EUAs for individual products[16]. Specific emergencies where emergency use authorizations are justified include:

1) A domestic emergency—or the potential for a domestic emergency—that involves increased risk of a biological, chemical, radiological, or nuclear agent attack
2) A military emergency—or the potential for a military emergency—that involves increased risk of military personnel being attacked using a biological, chemical radiological or nuclear agent(s), including those that are imminently life threatening and of particular risk to U.S. military forces
3) A public health emergency—or the potential for a public health emergency—that may affect national security or health of U.S. citizens living abroad and involves a biological, chemical, radiological, or nuclear agent, or a disease attributed to such agents
4) A material threat that may affect national security or the health and security of U.S. citizens living abroad

Clinical microbiology laboratories typically encounter EUAs during declared public health emergencies (PHE) when EUAs are issued for IVDs intended for the detection of the organism(s) responsible for the PHE.

The declaration of an emergency does not itself signal the ability to use EUAs; an additional declaration by the HHS Secretary is necessary to support their use. Emergency use authorizations of particular products are considered appropriate when: the agent involved in the emergency can cause a serious or life-threatening disease or condition; the product may be effective for the diagnosis, treatment, or prevention of the disease or condition caused by the agent; the known or potential benefits of the product outweigh the known or potential risks; and no alternative approved product to diagnose, treat, or prevent the disease or condition exists.

Recent infectious disease related PHEs where emergency use of IVDs was deemed justified can be viewed in **Table 1–2**.

EUAs for products are considered in effect until either the emergency or potential emergency no longer exists and the HHS terminates an EUA declaration, or until the product's approval status changes (e.g., the product obtains FDA clearance or approval for the relevant intended use), whichever is earlier (30).

What is test complexity?

CLIA regulations define three categories of test complexity (see 42 CFR §493.5) (1). From least to most complex, tests may be categorized as: waived tests, moderate-complexity tests (including Provider-Performed Microscopy (PPM) tests), or high-complexity tests. Laboratories may perform tests of only one complexity, or they may perform tests from any combination of complexities. The highest complexity test performed in a particular laboratory will determine the CLIA certificate the laboratory must obtain. For example, if a laboratory performs mostly waived testing but has one moderately complex test, that laboratory would be considered a moderate-complexity laboratory and must obtain the corresponding CLIA certificate (see Chapter 2 ***What are the types of CLIA certificates?***). In addition, laboratory personnel must meet specific

16 During the COVID-19 pandemic, the FDA oversight of LDTs with regard to EUAs went through several iterations. By August 2020, the FDA settled on an expectation that all COVID-19 tests, including LDTs, must be submitted to the FDA for emergency use authorization (30, 31). Given the updates issued through the FDA final rule, the FDA will likely continue to require submission of LDTs for EUA during future public health emergencies.

Table 1-2 Recent Public Health Emergencies with Emergency Use Declared for Infectious Disease Diagnostic Devices (31)

Year	Public Health Emergency	EUA Status
2022	Mpox Outbreak (Previously Monkeypox)	In Effect
2020	Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Outbreak	In Effect[1]
2016	Zika Virus Outbreak	In Effect
2015	Enterovirus D68 (EV-D68) Outbreak	Terminated (32)
2014	Ebola Virus Outbreak	In Effect
2013	Middle East Respiratory Syndrome (MERS) Outbreak	In Effect (Potential Emergency)
2013	Avian Influenza A (H7N9) Outbreak	In Effect (Potential Emergency)
2009 & 2010	2009 H1N1 Influenza Outbreak	Terminated (33)

[1] On May 11, 2023 the U.S. Department of Health and Human Services declared an end to the COVID-19 public health emergency (34). As of October 2024, the HHS Secretary has not terminated the EUA declaration. Therefore, existing EUAs for COVID-19 IVDs are still in effect and the FDA is currently able to grant new EUAs, although laboratories and manufacturers developing new COVID-19 diagnostics may be encouraged to submit new IVDs for premarket notification rather than for EUA (31).

qualifications depending on the complexity of tests performed in the laboratory (see 42 CFR §493 Subpart M – Personnel for Nonwaived Testing) (1).

For new tests, test complexity categorization is determined by the FDA during review of an individual test's premarket submission and is based on data submitted by the test manufacturer. The FDA is also responsible for notifying the manufacturer, CMS, and the CDC of their category determination (see 42 CFR §493.17(c)) (1, 35). If manufacturers disagree with the FDA determination, they may challenge the categorization by requesting a review of the decision (see 42 CFR §493.17(c)) and 21 CFR §10.75) (1, 36).

A test may be categorized as waived if it is cleared for at home or over the counter use, it employs simple and accurate methodologies such that erroneous results are unlikely, and/or it poses no reasonable risk of harm to the patient when used incorrectly (42 CFR §493.15(b)). Tests listed in 42 CFR §493.15(c) are also categorized as waived. Tests that do not meet the criteria in 42 CFR §493.15 are considered nonwaived and may be categorized as either moderate- or high-complexity tests (1). See Chapter 3 **Waived Testing** for additional information on waived tests.

Nonwaived test categorization is determined by assigning scores based on the following seven criteria (see 42 CFR §493.17)(1):

1) Knowledge: the scientific and technical knowledge required to perform the test
2) Training and experience: whether minimal or specialized training and experience are necessary to perform the test
3) Reagents and materials preparation: the stability of reagents and whether special handling or preparation is required
4) Characteristics of operational steps: whether operational steps are automatically executed and/or easily controlled, or require special monitoring or precise control
5) Calibration, quality control, and proficiency testing materials: whether materials are stable and reliably available
6) Test system troubleshooting and equipment maintenance: whether troubleshooting and maintenance require decision-making, intervention, and specialized knowledge and skills
7) Interpretation and judgement: whether minimal or extensive interpretation and judgement are necessary to perform the test and resolve problems

Scores between 1 and 3 are assigned for each criterion, with 1 representing the lowest level of complexity and 3 representing the highest level. Tests that receive a score of ≤12 are categorized as moderate complexity, while those receiving scores >12 are categorized as high complexity.

In some cases, tests initially categorized as moderately complex may meet the criteria for waived tests. In such instances, a CLIA Waiver by Application may be submitted to the FDA (35).

Is there a list of tests categorized by complexity?

There is a searchable database maintained by the FDA that provides information on tests categorized as waived, moderate complexity, or high complexity (37). When using the database, basic information about a particular test (e.g., manufacturer, analyte) may be input into the form to aid in narrowing down a search. The entire test list can also be viewed by clearing the form and clicking the search button. Additional information about the assays such as the manufacturer, analyte, and effective date can also be viewed on this database.

The searchable database can be accessed here: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm

Links to other searchable databases maintained by the FDA (e.g., 510(k), De Novo) are also available and can be found here: https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/medical-device-databases

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