The FDA Ruling on Laboratory Developed Tests

Taking Control of What's in Your Control

July 2024

Clinical and Laboratory Standards Institute (CLSI) is here to support laboratories with the tools, training, and expertise to navigate new regulatory oversight.

Updated 03 September 2024

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Taking Control of What's in Your Control

Since the final FDA ruling was published on 06 May 2024, there has been a great deal of discussion around the interpretation and implications of the new oversight, including more expansive commentary from the FDA. The final ruling declares the FDA's authority to regulate laboratory developed tests (LDTs) as medical devices under the Food, Drug, and Cosmetic Act (FDCA) and phases out the discretionary enforcement that has been in place since the law was first enacted in 1976.

Much of the discussion has continued to focus on concerns about the costs of the new regulation and how it might affect the availability and access to important diagnostic tests. The FDA has continued to express its concerns with the level of patient risk and exposure presented by LDTs, and has asserted the need for more oversight, pointing to the increasing complexity of instrumentation and software, as well as the expansion of use, as justification. And yet, there is still much to be defined in terms of how the ruling will be enforced.

CLSI has been engaging its constituency to better understand the biggest concerns, challenges, and impediments laboratories face as a result of the ruling. Here we discuss some preliminary results from a May 2024 survey of laboratorians affected.[1] This report will be part of an ongoing series sharing new insights, findings, and resources for laboratories navigating this new regulatory environment.

In early May, CLSI CEO Dr. Barb Jones offered a public statement reaffirming CLSI's commitment to supporting laboratories with the tools and resources they need to navigate any regulatory environment, including that resulting from this new LDT ruling.

"We are in this together. Since 1967, the expert volunteers of CLSI have provided the guidance that medical laboratories need to weather any storm...and we will weather this one together, again."

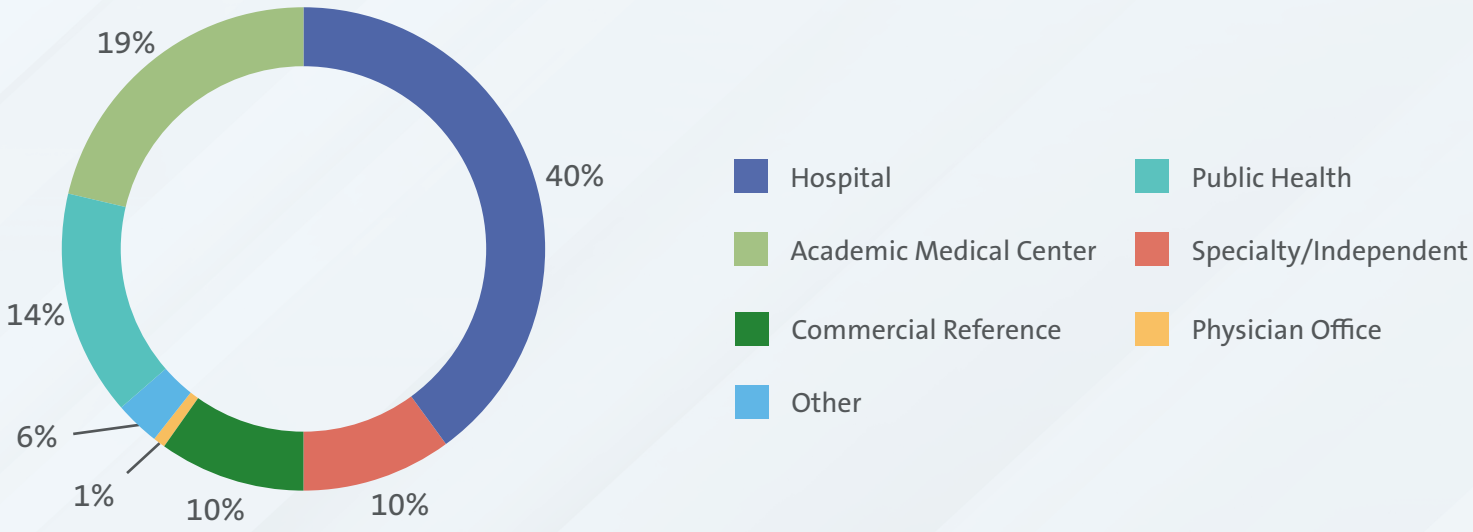
Reportedly, it is just 10 words that have changed. How is that causing so much turmoil?

The FDA is amending the definition of in vitro diagnostic (IVD) products to clarify that all IVD products are subject to oversight under the Food, Drug, and Cosmetic Act (FDCA), including when the manufacturer is a laboratory. Essentially, the FDA is stating that when it comes to diagnostic testing, laboratories are the same as other manufacturers of commercial IVDs, and LDTs are equivalent to IVD devices. That means that many, but not all, laboratories will have to meet FDA's registration requirements, premarket approvals, labeling, quality, and other validation protocols at the same level as manufacturers of traditional medical devices.

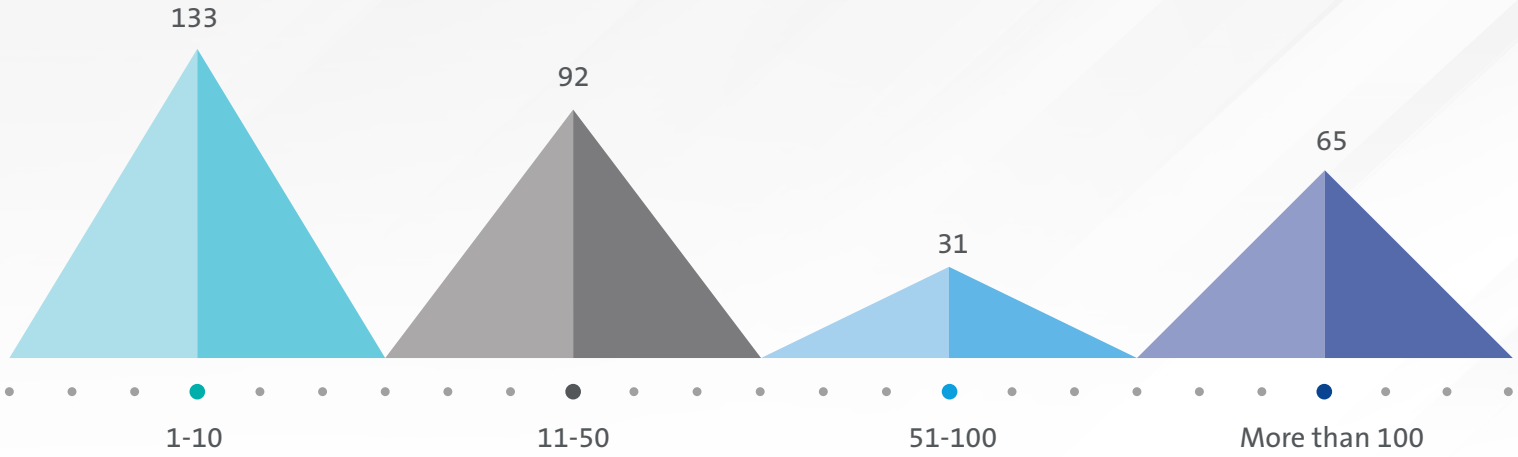
How many LDTs are there?

There are more than 12,000 laboratories in the US that run laboratory developed tests.[2] These include small independent facilities, hospital laboratories, academic medical centers, commercial reference laboratories, public health systems, and physician offices. Collectively, these laboratories are estimated to perform more than 3 billion tests per year.[2]

In what type of laboratory do you work?[3]

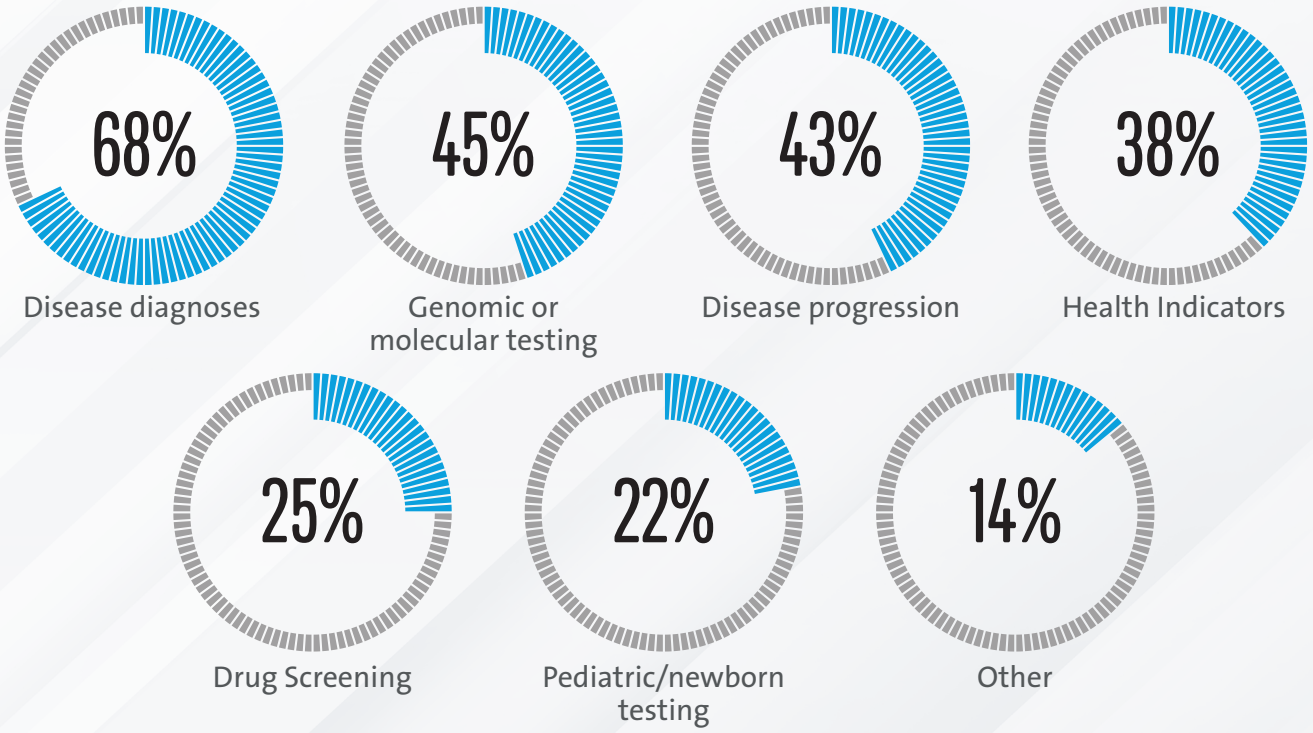


Many of these laboratories conduct just a handful of LDTs; however, some perform more than 100 different LDTs.[3]

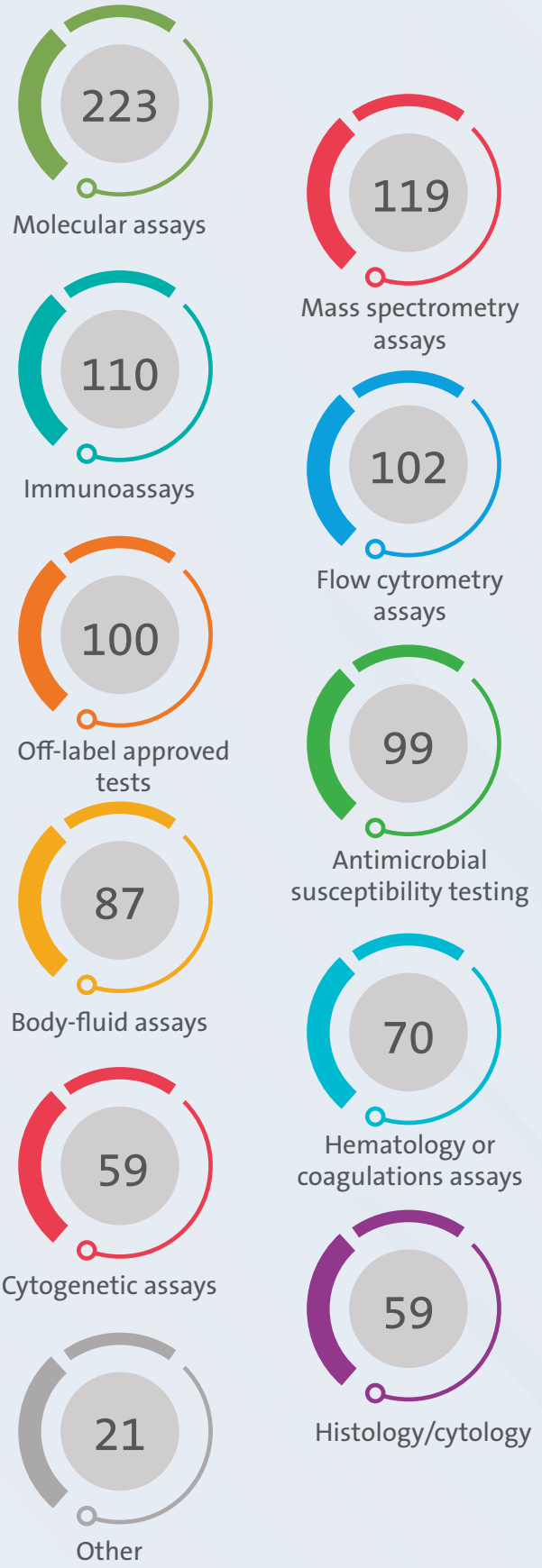


LDTs are mostly developed to support clinical diagnosis, monitor disease progression, aid in treatment response, and assist in drug screening.

What is the primary intent of your LDTs?[3]



What types of LDTs does your laboratory develop and/or utilize?[3]



Why is the FDA changing its regulatory enforcement now?

A different breed of tests

The discussion around FDA oversight has persisted for more than 30 years. The FDA contends that the LDTs of today are far different from those in the past. They are often run in high volume for large and diverse populations; involve complex technology, software, and artificial intelligence; are commonly marketed outside the immediate health care settings; and are used to diagnose or treat serious health conditions, such as cancer and heart disease.

Clinical Validity

The FDA has also raised concerns about a lack of data to support LDT clinical validity; that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. The agency has "received submissions for IVDs offered as LDTs showing that laboratories do not always properly validate tests or have sound clinical data to support a test's intended use" and has "seen modifications to tests that have not been supported by valid scientific evidence—for example, when there has been a lack of valid scientific evidence demonstrating the clinical validity of the modified test."

Analytical Validity

In addition, CLIA's analytical validation requirements are different from FDA's requirements. FDA's analytical validity review is more comprehensive than that of the CLIA program and focuses on safety and effectiveness, as opposed to whether the test detects the intended analyte when performed by the laboratory on patient specimens.[3]

Comparison: FDA versus CLIA / CMS oversight testing

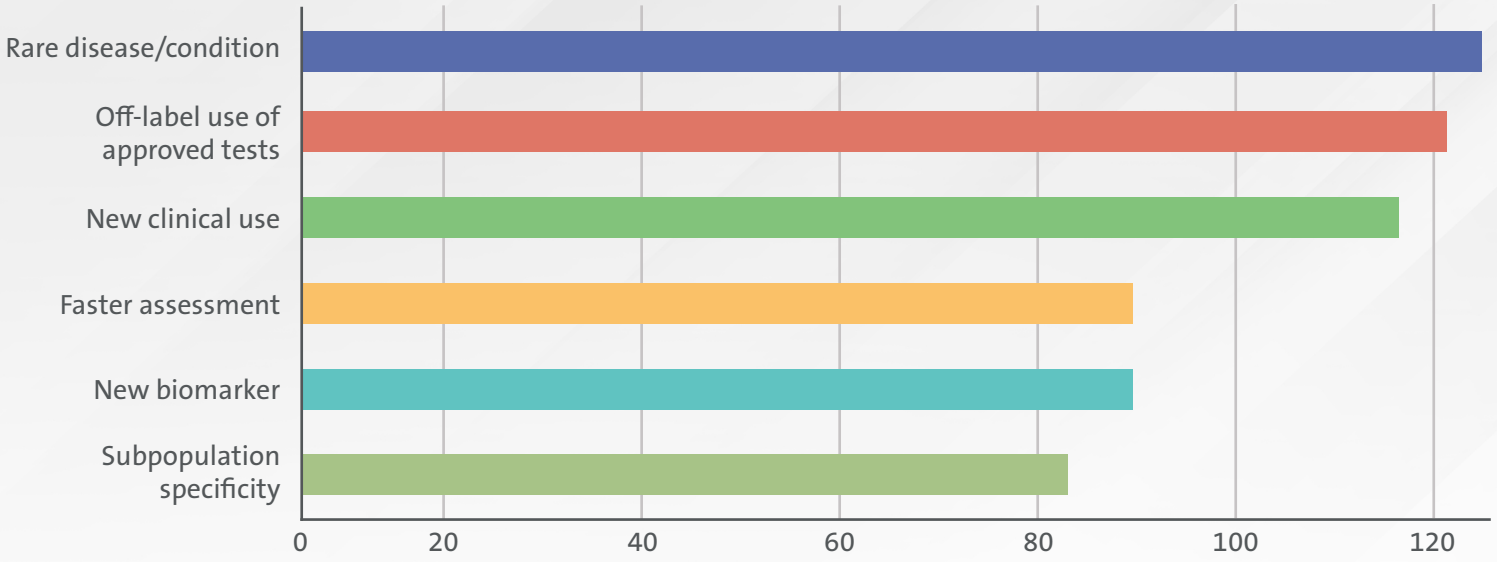
US FDA oversight	CLIA '88 / CMS oversight
Focus on devices themselves and how they perform	Focus on laboratory processes to use devices, not device quality
Review of analytic validity performed before test may be used on patients	Review of analytic validity performed during a 2 year inspection cycle; test may be in use for 2 years before assessment of data and test use
Analytic validity large in scope with thousands to tens of thousands of data points	Analytic validity may be performed on the smallest number of patients required for statistical significance
Requires assessment of clinical validity/utility testing	Does not require clinical validity/utility
Review requires assessment of patient safety	Review does not require assessment of patient safety
Required demonstration of effectiveness in determining presence/absence of condition being assessed	No required demonstration of effectiveness in determining presence/absence of condition being assessed
Requires adverse event reporting to identify inaccurate, unsafe, and ineffective devices	Does not require adverse event reporting
Requires removal of unsafe devices from market	Does not remove devices from the market

FDA: Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories - Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs). [March 2024]

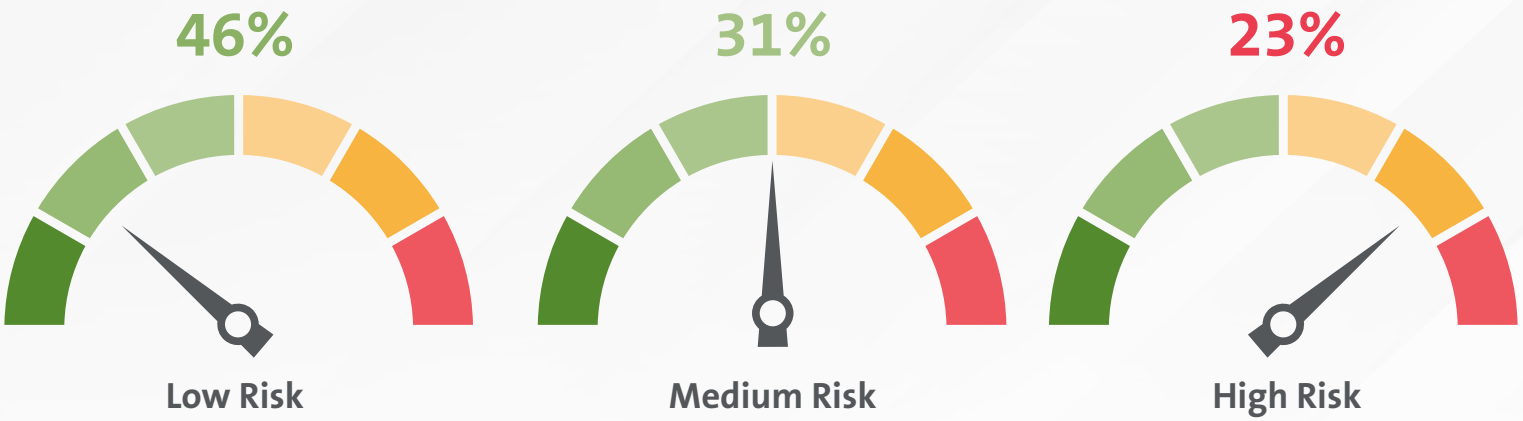
Although additional specificity and guidance are needed, the LDT Final Rule did provide some indication of the agency's thinking. The FDA states that:

> **"With respect to the consideration of peer-reviewed evidence, FDA would not expect laboratories to generate additional clinical validity data when available literature is adequate to demonstrate that the IVD is clinically valid."**

How are LDTs used today?[3]

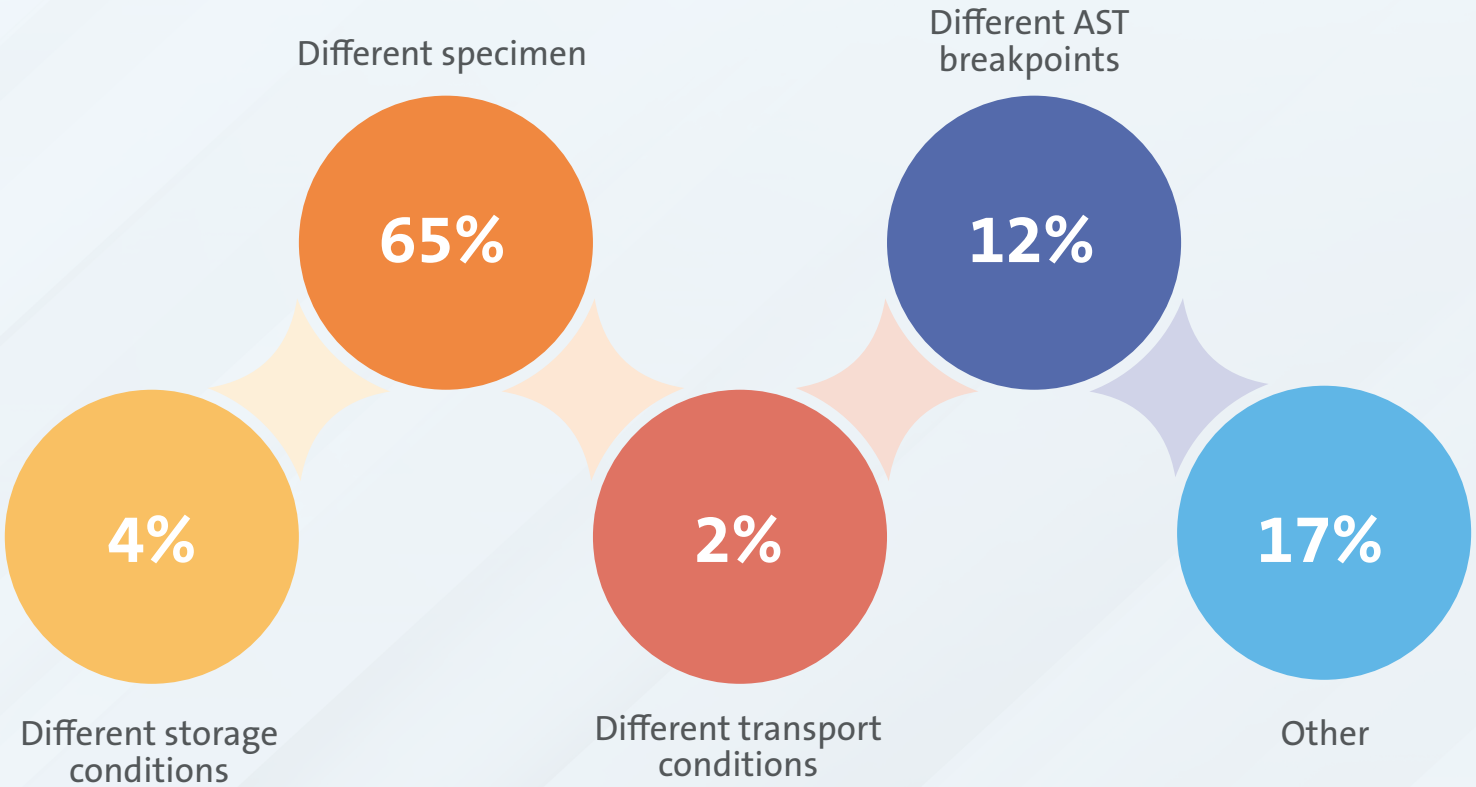


What types of laboratory developed tests are performed?[3] (Laboratory self-assessment of risk)

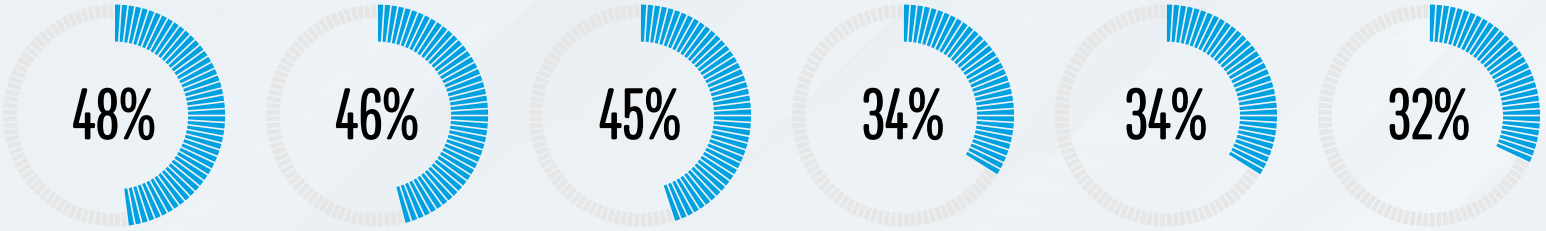


> "Why are LDTs important? LDTs are a critical way to approach many illnesses and commercial assays are often overpriced and out of reach for many."

What are the primary off-label uses for approved tests?[3]



Why LDT versus existing commercial test?[3]



Rare disease/ condition | Off-label use of approved test | New clinical use | New biomarker | Faster assessment | Subpopulation specificity

Are there LDTs that are "exempted" from regulation? What does "enforcement discretion" mean?

As an agency responsible for health and safety, the FDA can choose not to take enforcement action on certain requirements, allowing organizations to bypass typical regulatory pathways in specific circumstances. With the final rule, the FDA is choosing to phase out how it selectively exercises discretion over these tests, meaning that most LDTs will now be subject to a higher level of oversight and only a few categories will remain in the domain of "discretionary enforcement." Additionally, the FDA does have the right to change that practice at any time, without prior notice.

This concept is not new to LDTs. In 1992, the FDA declared its regulatory authority over LDTs (then called "home-brew assays") by issuing a draft guidance proposing to apply medical device regulations to these assays. This proposal was withdrawn based on objections from the laboratory community. The agency has chosen not to enforce that authority and has instead deferred to CLIA regulations requiring the establishment of performance specifications. However, in 1997 the FDA did exert some authority by publishing a Final Rule regulating analyte specific reagents (ASRs), which are components/reagents used in LDTs.[4]

Only select categories of LDTS will remain under the general enforcement discretion approach. These would include:

- **"1976-Type LDTs"** – These tests involve manual techniques, legally marketed components, and are performed in a CLIA-certified laboratory that meets requirements for high complexity testing.
- **Human leukocyte antigen tests** – These tests are used for organ, stem cell, and tissue transplants.
- **Forensic tests** – These tests are used solely for law enforcement purposes.
- **Tests manufactured and performed by the Department of Defense or Veterans Health Administration.**

All other LDTs will be subject to some level of new oversight per the staged phase-out schedule. However, currently marketed tests will not be required to conform with premarket review and QSRs as long as they are not modified after 06 May 2024.

What does it mean for LDTs to have labeling requirements?

The IVD labeling requirements under 21 CFR § 809.10 are highly detailed and do not translate well to tests that are not packaged and distributed. The FDA has committed to providing additional guidance prior to the implementation of this phase of the rollout (Stage II). Requirements for labeling of analyte specific reagents (ASRs) from the 1997 final rule are included in the current regulations, though it is difficult to determine which requirements might be considered for LDTs.

How soon will these regulations really take effect?

The new regulation is to be phased in over several years with high-risk tests being brought under review first.

Stage 1

By May 06, 2025

Compliance with

- Corrections & Removals **21 CFR Part 806**
- Medical Device Reporting **21 CFR part 803**
- Complaint Handling **21 CFR 820.198**

Stage 2

By May 06, 2026

Register with FDA, listing all LDTs

Compliance with

- Labeling Requirements **(21 CFR Part 801)**
- Investigational Device Requirements **(21 CFR Part 812)**

Stage 3

By May 06, 2027

Compliance with

- **QSRs in 21CFR Part 820**
- Design Controls **21 CFR 820.30**
- Purchasing Controls **21 CFR 820.50**
- Acceptance Activities **21 CFR 820.80** and **820.86**
- Corrective Actions **21 CFR 820.100**
- Records Management **21 CFR Part 820**

Stage 4

By November 06, 2027

Class III High Risk LDTs must apply for premarket approvals

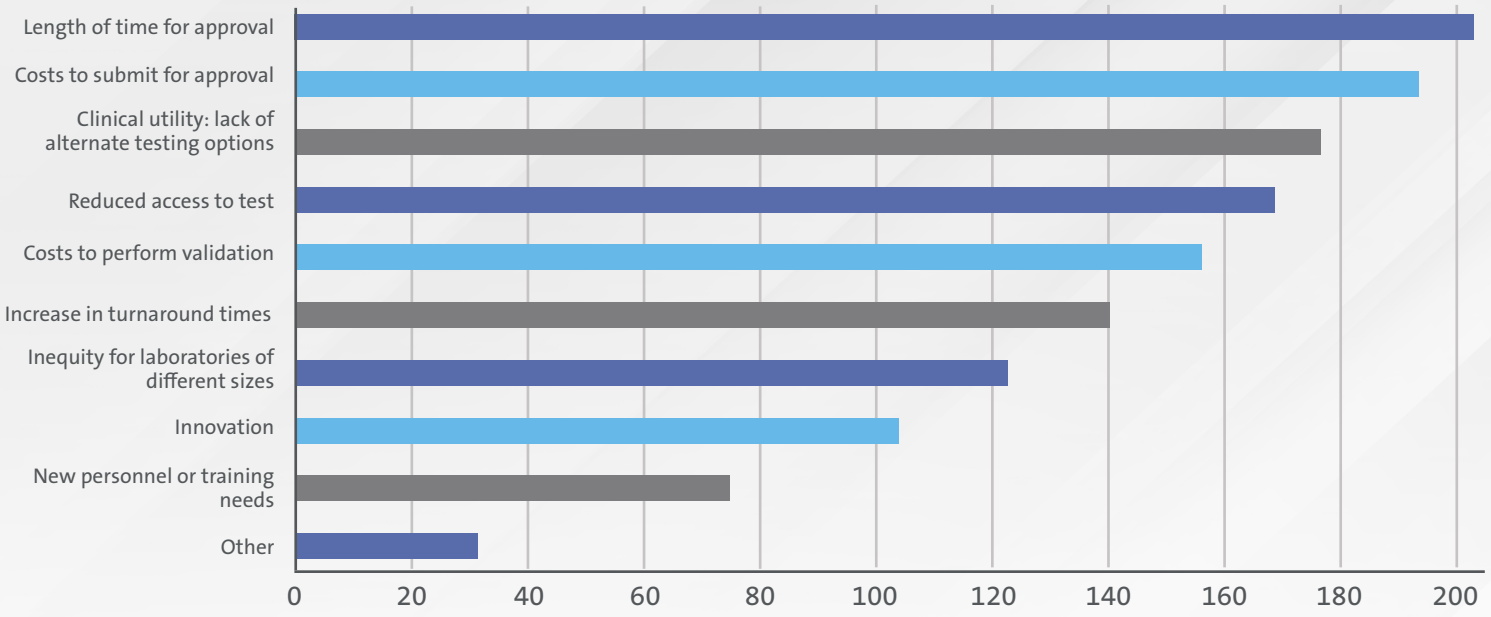
Stage 5

By May 06, 2028

Submit 510(k) or *de novo*

The FDA did reaffirm its intent to "down-classify" most LDT "high-risk" tests, meaning that more tests may not require full review (ie, PMA submission) until May 2028.

What are your laboratory's greatest concerns about the potential FDA ruling?[3]



What are the concerns of the laboratory community?

> *The cost of an FDA approval would effectively shut down any laboratory developed testing in our laboratory. Even the FDA fee for a far less expensive 510(k) clearance of around $15,000 would be burdensome, and a pre-market approval (PMA) with a fee of close to $400,000 and several million on testing costs and personnel would be a non-starter, meaning our patients would lack access to testing that benefits them most.*

> *Understanding FDA specifications. Although we believe we are fulfilling all requirements, we don't know how much the FDA would ask for rewording, restructuring of documents, etc., to meet their requirements.*

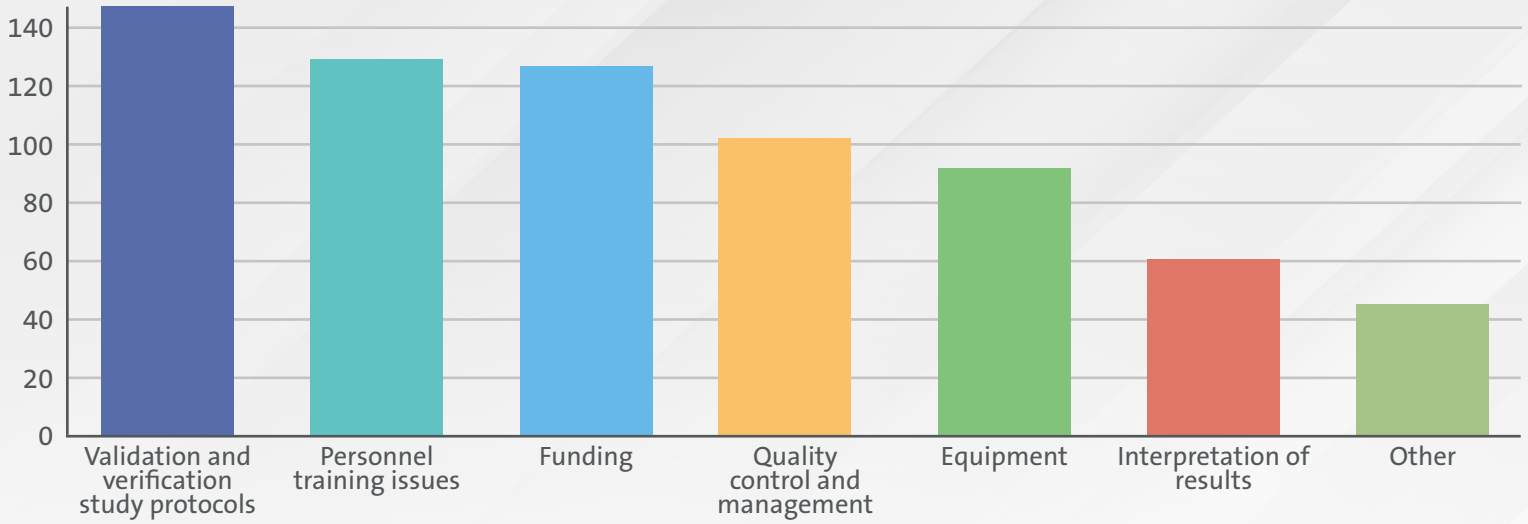
> *Failure to provide services for underserved and marginalized populations.*

> *FDA's inexperience with new testing methods.*

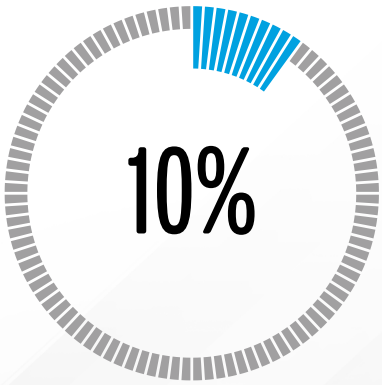
> *Cost, time, complexity of compliance with cGMP, and validation studies.*

> *Lack of validation material for rare diseases/organisms.*

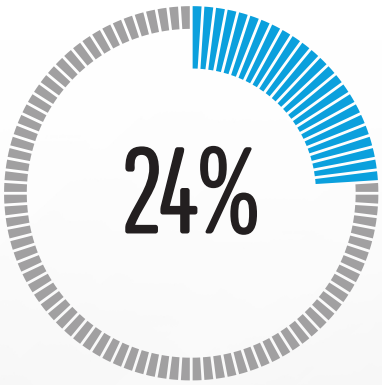
What are the primary challenges your laboratory currently faces in the development and implementation of LDTs?[3]



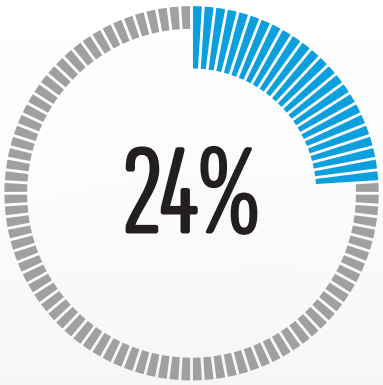
What is the laboratory's plan once the FDA ruling passes?[3]



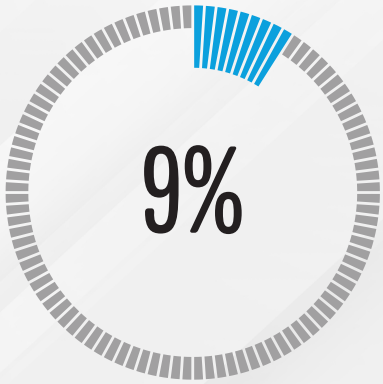
Discontinue offering the test(s)



Continue to offer LDTs, if financially feasible



Submit some or all LDTs to the FDA



Send LDTs to another facility

Unknown

The Path Forward

Understandably, laboratories are concerned about the additional FDA requirements for practices that are already in place to meet CLIA and/or accreditation requirements.

Fortunately, CLSI quality management and evaluation protocol standards have taken into consideration requirements from both CLIA and FDA, so applying these standards will help laboratories meet the FDA regulations.

In addition to concerns about requirements, many laboratory leaders are concerned about the costs of clearing the tests with FDA. Clearance of devices in the 510k Program, which is the FDA program that reviews devices that are "substantially equivalent" to those that are already FDA approved, incurs user fees of up to $5440 for small companies and $21,760 for large companies with revenue of more than $100 million.[5]

For most LDT developers—that is, developers that use their LDTs within their own health care system and are using them for testing that does not have an FDA-approved device, pre-market clearance of LDTs will not be required and a user fee will not be assessed. For developers that do not fall within the exempted categories, FDA has not clarified whether the user fees will be assessed at the same rates for traditional commercial device manufacturers.

What to do between now and next year when the first implementation phase goes into effect?

Prepare for change.

Recognize that while there are no restrictions taking effect for the next year, most LDTs will be subject to the quality requirements within the regulations eventually, some as early as next year.

– Download your free copy of **CLSI QSRLDT:** *Quality System Regulations for Laboratory Developed Tests: A Practical Guide for the Laboratory*

Understand the expectations.

More specifications will be released in the coming months, but in the interim laboratories can start identifying where they need to focus their attention based on the type of testing they are performing. CLSI has many resources to assist laboratories in meeting requirements.

FDA Requirement		Date goes into effect	CLSI Guidance Documents	Laboratory Developed Test (LDT) Type[a]				
				Unmet Need	Rare RBC Antigen	Currently Marketed-Unchanged	NY CLEP	New or Currently Marketed-But-Modified LDTs
MDR, Correction, Removal	§ 803	06 May 2025		**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
	§ 806			**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Complaint Files	§ 820.198		QMS11	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
			QMS14	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Registration	§ 807	06 May 2026		**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Listing	§ 807			**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Labeling	§ 809.10			**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Investigational Device	§ 812			**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Design Controls	§ 820.30	06 May 2027	EP05[b] EP06[b] EP07[b] EP09[b] EP12[b] EP17[b] EP21[b] EP24 EP25[b] EP27 QMS02 QMS13	No	No	No	**Yes**	**Yes**
Purchasing Controls	§ 820.50		QMS21	No	No	No	**Yes**	**Yes**
Acceptance Activities	§ 820.80 § 820.86		EP19 QMS18	No	No	No	**Yes**	**Yes**
CAPA	§ 820.100		EP18 EP23	No	No	No	**Yes**	**Yes**
Records	§ 820, subpart M		QMS02 QMS26				**Yes**	**Yes**
Premarket Review (high risk); PMA		06 November 2027		No	No	No	No	**Yes**
Premarket review (moderate/low risk); 510k and *de novo*		06 May 2028		No		No	No	**Yes**

[a] LDTs considered "exempt" from these requirements include: "1976-type" LDTs, HLA typing, Forensic testing, and LDTs performed by the VHA and DO.

[b] Denotes that the document has FDA recognition.

Start assessing gaps and determining a mitigation plan.

There are some meaningful unknowns—including potential litigation, congressional action regarding the VALID Act, and/or changes in political administration, any of which could affect the success and rollout of this ruling. These outcomes and when they will be determined is uncertain. It may not be time to fully operationalize, but it is time to assess and prepare. Some of the requirements are significant and will take time to successfully implement.

- Use the **CLSI Gap Analysis Tool** to take the first steps towards assessing quality systems in order to meet the requirements.
- Leverage the **CLSI Gap Analysis Checklist.** These 12 checklists provide a model for medical laboratories to organize the implementation and maintenance of an effective QMS.
- Continue to invest in building QMS capabilities. Ensure your laboratory is up to date with the newly updated **CLSI LQMS Certification Course.**

Ensure that your standard operating procedures (SOPs) and quality manual are updated and clearly define validation procedures for LDTs.

- Explore **CLSI EP19** to understand the framework of the evaluation protocol documents that clarify the requirements for validation of LDTs.
- Check out the **CLSI Method Navigator Tool** to understand what steps must be taken for validation and what guidance will help with proper implementation.

Begin anticipating premarket approvals for any new tests in development.

- Stay current with additional training, guidance, and member updates and resources from CLSI. **Become a CLSI Member** and subscribe to the LDT interest group.
- If you are developing LDTs using next generation sequencing (NGS), use **CLSI MM09 |** *Human Genetic and Genomic Testing Using Traditional and High-Throughput Nucleic Acid Sequencing Methods,* 3rd Edition to design any new validation studies. CLSI MM09 covers the entire test lifecycle and incorporates clinical validity assessment into NGs test development and content design.
- For validation of breakpoints used in antimicrobial susceptibility testing (AST), start with **CLSI M52 |** *Verification of Commercial Microbial Identification and Antimicrobial Susceptibility Testing Systems,* 1st Edition, and **CLSI M02 |** *Performance Standards for Antimicrobial Disk Susceptibility Tests,* 14th Edition and/or **CLSI M07 |** *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically,* 12th Edition, until the FDA provides clear guidance on enforcement discretion for LDTs for unmet needs.

References

1 Clinical and Laboratory Standards Institute Member and User Survey, May 2024 (262 participants). Respondents included laboratory directors, managers, scientists, medical directors, pathologists, clinicians, and other pathologists, all belonging to a laboratory currently offering LDTs as of May 2024.

2 Pew Charitable Trusts (2021).

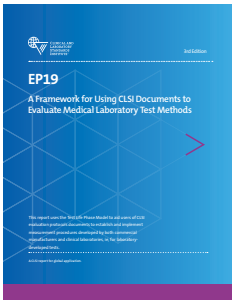
3 LDT behavior and perceptions collected via CLSI member survey, May 2024 (n=262).

4 US FDA. Draft Guidance for Industry, Food and Drug Administration Staff and Clinical Laboratories. *Framework for Regulatory Oversight of 7 Laboratory Developed Tests (LDTs).* Accessed 4 March 2024.

5 CLIA Verification of Performance Specifications (cms.gov) 42 CFR § 493.1253 - Standard: Establishment and verification of performance specifications. Medical devices; classification/reclassification; restricted devices; analyte specific reagents--FDA. *Final rule.* Fed Regist. 1997 Nov 21;62(225):62243-60. PMID: 10177056.

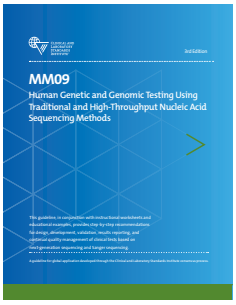
6 Medical Device User Fee Amendments (MDUFA), FY 2024 fees.

CLSI has many resources to help laboratories assess, plan, and prepare.



CLSI EP19 | *A Framework for Using CLSI Documents to Evaluate Medical Laboratory Test Methods,* 3rd Edition

This report introduces the Test Life Phases Model, which points users to CLSI evaluation protocol documents to establish and implement commercially manufactured or LDT methods.

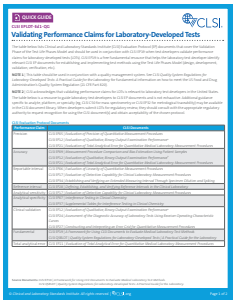


CLSI MM09 | *Human Genetic and Genomic Testing Using Traditional and High-Throughput Nucleic Acid Sequencing Methods,* 3rd Edition

This guideline, in conjunction with instructional worksheets and educational examples, provides step-by-step recommendations for design, development, validation, results reporting, and continual quality management of clinical tests based on next-generation sequencing and Sanger sequencing.

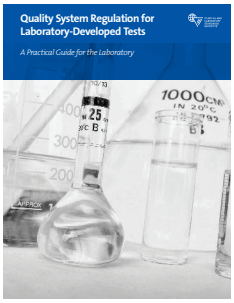
LQMS
Laboratory Quality Management System

This newly redesigned and streamlined LQMS program (2024) features engaging interactive elements and specific step-by-step instructions to help navigate regulatory and accreditation requirements. The program includes easy-to-navigate lessons for each of the 12 Quality System Essentials (QSEs) in the Quality Management System (QMS) model presented in CLSI guideline QMS01—A Quality Management System Model for Laboratory Services.



NEW! CLSI EP Quick Guide

Overview of CLSI evaluation protocol standards necessary for validation of an LDT.

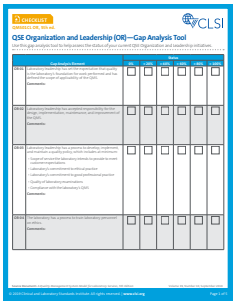


CLSI QSRLDT

This practical guide is intended for the laboratory that is creating LDTs that are subject to the FDA regulations, specifically the Quality System Regulation (QSR), 21 CFR Part 820. (Update available late summer)

METHOD Navigator

Interactive tool that enables easy access to CLSI standards to support the establishment and implementation of LDTs or implementation of any regulatory-approved commercial test methods.



CLSI Gap Analysis Checklist

These 12 checklists provide a model for medical laboratories to organize the implementation and maintenance of an effective QMS.

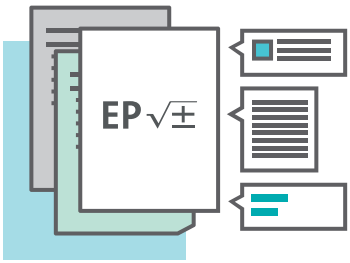
GAP Analysis

Helps personnel quickly and easily assess whether their laboratory follows QMS requirements and can help track progress toward achieving complete compliance.

CLSI Call for Volunteers!

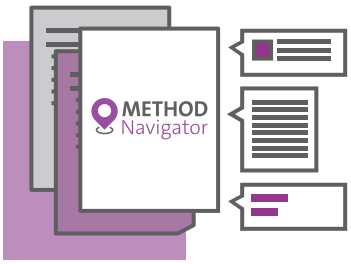
> *If you're a person who cares about laboratory medicine, about the quality of the results that get to the patient...you really need to volunteer.*

Are you passionate about advancing medical laboratory guidelines for evaluation protocols? Your expertise is needed! There has never been a more important time to join a working group.



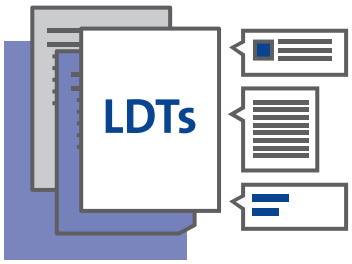
Working Group for EP Reviewers

Looking for expertise in linearity, establishment of reference intervals, ROC curves, surrogate samples, interference testing, lot-to-lot variation, qualitative tests, reagent stability, delta checks, extended measuring intervals, commutability, precision, and sample stability. Join our EP Working Group!



Method Navigator Reviewer Group

Seeking volunteers who are well-versed in FDA quality system regulations and CLIA requirements. Your expertise is invaluable and could help us maintain and enhance our comprehensive and newly updated EP navigation tool, Method Navigator.



Laboratory-Developed Test Final Rule Advisory Group

CLSI is forming a special advisory group to leverage the expertise of our laboratory, industry, and government subject matter experts to help inform CLSI responses including organizational strategy, product development, communications and collaboration opportunities.

To apply or for more information visit **clsi.org/volunteer.**

Don't see a good fit? Visit CLSI.org for other opportunities and ways to participate.

Streamline the FDA Approval Journey:

A Panel Discussion with the FDA, CLSI, and Abbott Laboratories

WEBINAR: Wednesday, August 28th

With speakers including:

Dr. Barb Jones, CEO, CLSI

Vicki Petrides, MS, Abbot Laboratories

Dr. Terry Woods, Director, Divisions of Standards & Conformity Assessment, FDA

Navigating the FDA device approval and clearance process can be daunting. However, the appropriate use of consensus standards can greatly reduce the burden for the conformity assessment elements of medical device submissions. By using declarations of conformity (DOC), particularly with FDA-recognized standards, device developers and manufacturers can streamline submission preparation.

Price: Free
Earn 1.0 P.A.C.E.® credits.

This session will fill up quickly. Be sure to **register today** and save your spot!

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