Update on the Regulation of LDTs: FDA, VALID Act, CLIA Modernization, and More

Sponsored by the ACMG Advocacy and Government Affairs Committee

May 21, 2024, 2:00pm-3:00pm ET

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

Disclosures

Sarah South, PhD, FACMG

ACMG Board of Directors

Disclosure: Employed by Quest Diagnostics

Michelle McClure, PhD

ACMG Director of Public Policy

Disclosure: None

Marco Leung, PhD, FACMG

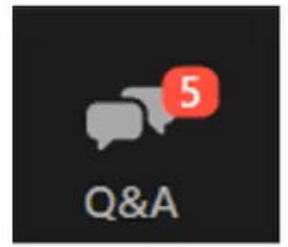
Chair, ACMG Advocacy and Government Affairs Committee

Disclosure: None

A recording of the webinar will be made available in the ACMG Genetics Academy.

Educational credits are not offered for this webinar.

Q&A



To submit a question please use Q&A feature.

- Use Chat ONLY for indicating technical issues
- To help prioritize a question (called upvoting), give it a thumbs up

The content of today's webinar is for informational purposes only. It is not intended as a guide for complying with FDA regulations. Laboratory professionals should consult with their regulatory affairs experts for guidance on complying with FDA requirements.

FDA's New Rule on Regulation of LDTs

How Did We Get Here?

- CLIA 1967
- Medical Device Amendments of 1976
- CLIA 1988
- (Enforcement discretion?)
- 2014 – FDA draft guidances
- 2022 – VALID Act
- 2023 – FDA Proposed Rule
- 2024 – FDA Final Rule

Device means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

> […] (B)intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals […]

Full definition at 21 U.S. Code § 321(h)(1)

ACMG Engagement Every Step of the Way

- 2014 FDA guidances
- DAIA & early versions of VALID Act
- VALID 2021-2022:
  - Hill meetings, letters, and emails
  - Member engagement
  - Grassroots campaigns (hundreds of letters sent in 2022)
  - Congressional briefing
- FDA rule:
  - Public comments to FDA
  - Hill meetings
  - White House Offices
  - OIRA meetings

The New FDA Rule

- Regulatory change is 10 words:
  - IVDs are devices under the FD&C Act "**including when the manufacturer of these products is a laboratory**"
  - Phaseout of "enforcement discretion"; 5 phases beginning May 6, 2025 with full enforcement by May 6, 2028
  - Exceptions/new enforcement discretions
- Means that:
  - Manufacturer includes laboratories
  - Device/IVD includes LDTs

Timeline of Implementation

- Stage 1, beginning May 6, 2025:
  - Medical device reporting (MDR) requirements, correction and removal reporting requirements, and complaint files requirements
- Stage 2, beginning May 6, 2026:
  - Requirements not covered during other stages of the phaseout policy, including registration and listing, labeling, and investigational use requirements
- Stage 3, beginning May 6, 2027:
  - Quality systems (QS) requirements
  - FDA also expects laboratories to retain manufacturing records they may already have or may create for certain IVDs prior to stage 3 of the phaseout policy

Timeline of Implementation

- Stage 4, beginning November 6, 2027:
  - Premarket review requirements for high-risk IVDs offered as LDTs
    - Premarket approval (PMA) applications
  - If a premarket submission has been received by the beginning of this stage, FDA intends to continue to exercise enforcement discretion for the pendency of its review
- Stage 5, beginning May 6, 2028:
  - Premarket review requirements for moderate-risk and low-risk IVDs offered as LDTs
    - Premarket notifications (510(k) applications) and *de novo* classification requests
  - If a premarket submission has been received by the beginning of this stage, FDA intends to continue to exercise enforcement discretion for the pendency of its review

Medical Device Regulations

Medical Device Regulations

Stage 1 (May 6, 2025)

- Medical device reporting (MDR) – 21 CFR Part 803
  - Identify and monitor adverse events (deaths and serious injuries) and certain device malfunctions in a timely manner
  - Includes reporting and record keeping requirements
- Corrections & Removals – 21 CFR Part 806
  - Recalls (generally voluntary) of defective or problematic tests
  - Class I, II, or III recalls
- Complaint Handling – 21 CFR 820.198
  - Procedures for receiving and evaluating complaints
  - Includes any written, electronic, or oral communication alleging deficiencies related to identity, quality, durability, reliability, safety, effectiveness, or performance

Medical Device Regulations

Stage 2 (May 6, 2026)

- Registration & listing – 21 CFR Part 807
  - Register establishment (annual fee)
  - List all tests
- Labeling – 21 CFR Part 801 and 21 CFR Part 809
  - Labels: Physical labels on device/packaging
  - Labeling: All other written, printed, or graphic matter accompanying the device (e.g., posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc.)
  - Advertising: Appellate court decision that most, if not all advertising, is labeling
- Investigational device exemptions – 21 CFR Part 812
  - Significant risk – must apply for an IDE
  - Nonsignificant risk – requires IRB approval

Medical Device Regulations

Stage 3 – QS Regulations (May 6, 2027)

- General provisions – 21 CFR Part 820, Subpart A
- QSRs – 21 CFR Part 820, Subpart B
- Design controls – 21 CFR Part 820, Subpart C
- Document controls – 21 CFR Part 820, Subpart D
- Purchasing controls – CFR Part 820, Subpart E
- Identification and traceability – 21 CFR Part 820, Subpart F
- Product and process controls – 21 CFR Part 820, Subpart G
- Acceptance activities – 21 CFR Part 820, Subpart H
- Nonconforming product – 21 CFR Part 820, Subpart I
- Corrective and preventive action (CAPA) – 21 CFR Part 820, Subpart J
- Labeling and packaging control – 21 CFR Part 820, Subpart K
- Handling, storage, distribution, and installation – 21 CFR Part 820, Subpart L
- Records – 21 CFR Part 820, Subpart M
- Servicing – 21 CFR Part 820, Subpart N
- Statistical Techniques – 21 CFR Part 820, Subpart O

Medical Device Regulations

Stage 4 (November 6, 2027)

- Premarket approval (PMA) – 21 CFR Part 814
  - Non-clinical laboratory studies: information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests
  - Clinical investigations: study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations

Medical Device Regulations

Stage 5 (May 6, 2028)

- Premarket notification (510(k)) – 21 CFR Part 807, Subpart E
  - Substantial equivalence – new device is as safe and effective as the legally marketed predicate
  - Comparisons – e.g., intended use, technical characteristics, may include non-clinical and/or clinical performance data
- *De novo* classification requests – 21 CFR Part 860, Subpart D
  - Clinical and non-clinical data

Medical Device Regulations

Test Classification

- 21 CFR Part 860
  - Class I – general controls
    - i.e., sections 501 (adulteration), 502 (misbranding), 510 (registration), 516 (banned devices), 518 (notification and other remedies), 519 (records and reports), and 520 (general provisions)
  - Class II – special controls
    - General controls alone are insufficient
    - Sufficient information exists to establish special controls (e.g., performance standards, post market surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions deemed necessary)
  - Class III – premarket approval
    - General controls are insufficient, or application of special controls in addition to general controls would provide such assurance, but the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury
- FDA database on medical device classification

Regulatory Fees

Based on FY 2024

- Registration Fees (per establishment):
  - Annual fee of $7,653
- User Fees (per test):

Application Type	Standard Fee	Small Business Fee
510(k)	$21,760	$5,440
PMA, PDP, PMR, BLA	$483,560	$120,890
De Novo Classification Request	$145,068	$36,267
Annual Fee for Periodic Reporting on a Class III device (PMAs, PDPs, and PMRs)	$16,925	$4,231

- Small business:
  - Defined as a business, including its affiliates, whose gross receipts and sales are less than $100 million for the most recent tax year.
  - Must have an approved Small Business Determination (SBD) from FDA.
  - Additional waivers available for small businesses with gross receipts or sales of $30 million or less

Exceptions to the Regulations

(Enforcement Discretions)

Enforcement Discretions

	Stage 1 MDR, correction & removal reporting, complaint files	Stage 2 Registration/listing, labeling, investigational use, other requirements not covered in other stages	Stage 3 QS Requirements	Stage 4 Premarket review for high-risk LDTs	Stage 5 Premarket review for moderate-risk & low-risk LDTs
1976-Type LDTs	Exempt	Exempt	Exempt	Exempt	Exempt
HLA LDTs for allele typing associated with transplantations	Exempt	Exempt	Exempt	Exempt	Exempt
Forensic tests	Exempt	Exempt	Exempt	Exempt	Exempt
DoD/VHA	Exempt	Exempt	Exempt	Exempt	Exempt
NYS CLEP	May 6, 2025	May 6, 2026	May 6, 2027	Exempt	Exempt
Unmet need of patients receiving care within the same healthcare system	May 6, 2025	May 6, 2026	Most exempt	Exempt	Exempt
LDTs offered prior to 5/6/2024 & unmodified	May 6, 2025	May 6, 2026	Most exempt	Exempt	Exempt
Non-molecular antisera LDTs for rare RBC antigens	May 6, 2025	May 6, 2026	Most exempt	Exempt	Exempt
All other LDTs	May 6, 2025	May 6, 2026	May 6, 2027	November 6, 2027	May 6, 2028

NYS CLEP

No enforcement of premarket review requirements for:

- LDTs that are approved by the New York State Department of Health's Clinical Laboratory Evaluation Program (NYS CLEP)
  - Includes NYS CLEP-approved high-risk tests and moderate-risk tests that have either full approval or conditional approval
  - However, if conditional approval is withdrawn (e.g., because NYS CLEP approval is denied), then the test would have to go through premarket approval by FDA
  - Other regulatory requirements still required
    - E.g., QS requirements, registration and listing, labeling, MDR requirements, etc.

Unmet Need

No enforcement of premarket review and most QS requirements for:

- Validated LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within that same healthcare system
- Unmet need means there is no available FDA-authorized IVD that meets the patient's needs
- This may be because:
  - there is no FDA-authorized IVD for the disease or condition
  - there is an FDA authorized IVD for the disease or condition but it is not indicated for use on the patient, or a unique attribute needs to be added to the LDT to meet the patient's needs (e.g., different specimen type)
  - there is an FDA-authorized IVD but it is not available to the patient

Unmet Need

- Does not include patients that are being treated at an affiliated hospital with different corporate ownership than the laboratory
- Does not apply when there is an available FDA-authorized IVD that would sufficiently meet the needs of the patient
  - e.g., potential improvements in performance to an FDA-authorized IVD does not fall within this exemption
- Other regulations, such as MDR, correction & removal reporting, complaint files, registration & listing, and labeling will still be enforced; also includes records requirements (under QSRs)
  - FDA also intends to request that laboratories offering an LDT under this exemption submit certain labeling information

“Grandfathering”

No enforcement of premarket review and most QS requirements for:

- Currently marketed IVDs offered as LDTs that were first marketed prior to May 6, 2024 (the date of issuance of the final rule)
- Other regulations, such as MDR, correction & removal reporting, complaint files, registration & listing, and labeling will still be enforced; also includes records requirements (under QSRs)
  - FDA also intends to request that laboratories offering an LDT under this exemption submit certain labeling information

“Grandfathering”

- After May 6, 2024, the following modifications would trigger full compliance:
  - changes to the indications for use (e.g., specimen types, intended patient population)
  - changes to the operating principal of the test (e.g., changes to critical reaction components)
  - inclusion of significantly different technology in the test (e.g., addition of AI or machine learning algorithms, changing from targeted sequencing to whole genome sequencing, changing from manual to automated procedures)
  - modifications that adversely change the performance or safety specifications

Modifications to Legally Marketed IVDs

- No premarket review requirements for changes to another manufacturer's legally marketed test when the following criteria are met:
  - the laboratory is certified by CLIA to perform high complexity testing;
  - the original test is legally marketed following 510(k) clearance or de novo authorization;
  - the laboratory complies with design controls and other QSRs;
  - the modification does not significantly affect the safety or effectiveness of the test;
  - the modification does not constitute a major change to the intended use; and
  - the modified test is only used in the laboratory that made the modification.

Note: This information is not listed under the enforcement discretion section of the final rule. Instead, this information is in section V.C.4. which explains the stages of the phaseout policy.

RBC Antigens

No enforcement of premarket review and most QS requirements for:

- Non-molecular antisera LDTs for rare red blood cell (RBC) antigens when such tests are manufactured and performed by blood establishments, including transfusion services and immunohematology laboratories and when there is no alternative IVD available to meet the patient's need for a compatible blood transfusion
- Does not apply to molecular tests for genotyping RBC antigens

1976-Type LDTs

No enforcement of any requirements for:

- "1976-Type LDTs"
  - Includes tests with the following characteristics:
    - use of manual techniques (without automation) performed by laboratory personnel with specialized expertise;
    - use of components legally marketed for clinical use; and
    - design, manufacture, and use within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing
  - Examples:
    - Would include immunohistochemistry tests that involve no automated preparation or interpretation
    - Would NOT include lateral flow tests as they do not generally rely on laboratory personnel expertise

HLA Tests, Forensics, DoD/VHA

No enforcement of any requirements for:

- Human leukocyte antigen (HLA) tests that are designed, manufactured, and used within a single laboratory certified under CLIA for high complexity histocompatibility testing when used in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing, for HLA antibody screening and monitoring, or for conducting real and “virtual” HLA crossmatch tests
- Tests intended solely for forensic (law enforcement) purposes
- LDTs manufactured and performed within the Department of Defense (DoD) or Veterans Health Administration (VHA)

Test Not Impacted by Rule

…because regulations were already being enforced

- Tests required for infectious disease screening of blood donors or HCT/P (human cells, tissues, and cellular and tissue-based products) donors under 21 CFR 610.40 and 21 CFR 1271.80(c), respectively
- Tests required for determination of blood group and Rh factors under 21 CFR 640.5
- Tests intended for emergencies, potential emergencies, or material threats declared under section 564 of the FD&C Act
  - FDA also released two draft guidances related to IVDs in response to an emergent situation and during a declared public health emergency (public comments due by July 5, 2024)
- Direct-to-consumer tests intended for consumer use without meaningful involvement by a licensed healthcare professional

Caveats

- The FDA could change their enforcement discretion policies at any time, without going through the rulemaking process.

- FDA notes that it retains the discretion to pursue enforcement action at any time against violative IVDs when appropriate, regardless of whether they fall under an exempted category.

Looking Ahead

Clarity on FDA Rule

- FDA expected to provide more targeted guidance and/or make additional resources available on specific topics
- Examples of areas that may need clarification:
  - Labeling requirements – Since LDTs are not packaged and distributed, many IVD labeling requirements do not translate well
  - WGS – How will FDA view the intended use for WGS for rare diseases vs. usage of WGS as backbone for genome-sliced panel testing?
- Stakeholders should communicate to FDA about where additional clarity is needed
  - Feedback to ACMG (advocacy@acmg.net)
  - Direct outreach to FDA (LDTFinalRule@fda.hhs.gov)

Congressional Intervention

CRA and Appropriations

- Congressional Review Act (CRA)
  - Method by which Congress can stop an Agency rule from going into effect
  - Requires a majority vote in both chambers of Congress
  - Senator Paul and Representative Finstad planning to introduce the CRA resolutions
  - ACMG doing targeted outreach to generate support prior to introduction
  - Labs/institutions encouraged to also engage
  - Grassroots (individual) engagement opportunities to be announced after resolutions are introduced
- Appropriations (federal funding approved by Congress)
  - Potential restrictions on use of appropriated funds to implement the rule
  - If passed, would be part of the FY 2025 appropriations

Congressional Intervention

New Legislation

- VALID Act (or something similar)
  - Introduced in House but no Senate companion to date
    - No republican lead sponsor in Senate
  - Potential new legislation that would be similar to VALID but rebranded under a new name
- CLIA modernization legislation
  - Looking for lead sponsors
  - Would modify CLIA regulations and make clear that LDTs are clinical procedures regulated by CLIA, not FDA
- No clear path for passing legislation this Congress although there is a good bit of attention to the topic in both the House and Senate
  - E.g., Recent House E&C hearing; Senator Cassidy's RFI

Legal Challenges

- Questions remain over FDA's legal authority to regulate LDTs as medical devices
- Legal challenges expected but not guaranteed
- Lawsuit may or may not result in delay of implementation of the rule

Take Aways

- While there are numerous paths to potentially stop implementation of the rule, it is unclear if any of those will be successful
- Laboratories should familiarize themselves with the details of the new rule and medical device regulations
- Connect with regulatory affairs professionals
- Explore available resources:
  - CDRH Learn – https://www.fda.gov/training-and-continuing-education/cdrh-learn
  - ACMG Summary with Regulatory References – https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/Laboratory_Developed_Tests_LDTs_.aspx

Questions?

Contact ACMG:

advocacy@acmg.net

How is the FDA rule impacting your lab's test offerings?

Share your stories with ACMG – advocacy@acmg.net