Decoding FDA's New Final Rule on Laboratory Developed Tests

What's Next?

Carolina M. Wirth & Melissa L. Markey

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ADVISORY SERVICES

HALL RENDER
KILLIAN HEATH & LYMAN

Presenters

Carolina M. Wirth

Shareholder

cwirth@hallrender.com

(202) 780-2989

Melissa L. Markey

Shareholder

mmarkey@hallrender.com

(248) 310-4876

Background

1. What are Laboratory Developed Tests (LDTs)?
2. How has the FDA regulated LDTs historically?
3. What are FDA's concerns regarding LDTs?

Laboratory Developed Tests (LDTs)

- FDA has generally considered an LDT to be an *in vitro* diagnostic (IVD) that is:
  - Intended for clinical use
  - Designed, manufactured, and used within a single laboratory that is CLIA-certified for high complexity testing
- Historically, LDTs were mostly:
  - Manufactured in small volumes
  - Administered in controlled clinical settings
  - Used for diagnosing rare diseases or meeting the specialized needs of a local patient population

FDA's General Enforcement Approach

- According to FDA, LDTs fall under the Medical Device Amendments of 1976 (MDA)
- However, FDA has historically exercised enforcement discretion for most LDTs
  - "Enforcement discretion" means FDA generally has chosen not to enforce MDA's requirements with respect to LDTs
  - Such requirements relate to registration and listing, reporting adverse events to FDA, current good manufacturing practices, and premarket review

FDA's Concerns Regarding Modern LDTs

- FDA believes the risks associated with many modern LDTs are much greater than the risks associated with the LDTS for which enforcement discretion was originally intended
- Modern LDTs are increasingly complex, used more widely and for more diverse populations, frequently manufactured by large commercial laboratories and marketed nationwide, and more often used in screening and diagnosis
- FDA has also warned of potentially inaccurate, unsafe, ineffective or poor quality IVDs offered as LDTs that caused or may have caused patient harm

VALID Act

Verifying Accurate Leading-Edge IVCT Development (VALID) Act

- Bipartisan legislation introduced in 2021 to statutorily grant FDA the authority to regulate LDTs
  - Created a new product category called in vitro clinical tests (IVCT)
  - Outlined a risk-based approach to regulation
  - Grandfathered all current tests on the market
- Failed to be included in the 2023 Consolidated Appropriations Act

FDA Final Rule

1. What did FDA change?
2. What is the final “phased-out” policy?
3. What are the limited enforcement discretion categories?

What did FDA change?

- FDA amended the definition of an IVD in 21 C.F.R. § 809.3(a) to explicitly state that IVDs are devices under the Federal Food, Drug, and Cosmetic Act:

> (a) **In vitro diagnostic products are these reagents, instruments, and systems intended for use in the diagnosis of disease** or other conditions, including a determination of the state of health, in order to cure, mitigate, treat or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) 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.***

What did FDA change? (Cont.)

- Going forward, in a phased-process, FDA will regulate LDTs "*under the same enforcement approach*" as IVDs, meaning the agency will enforce applicable requirements related to:
  - Registration and listing (21 C.F.R. Part 807)
  - Reporting adverse events to FDA (21 C.F.R Part 803)
  - Current good manufacturing practices (GMPs) (21 C.F.R. Part 820)
  - Premarket review
    - Premarket approval (PMA) applications
    - 510(k) or De Novo

Final "Phased-Out" Policy

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
1 Year May 6, 2025	**2 years May 6, 2026**	**3 years May 6, 2027**	**3.5 years November 6, 2027**	**4 years May 6, 2028**
• Medical Device Reporting (MDR) - 21 C.F.R. § 803 • Correction and Removal Reporting – 21 C.F.R. § 806 • Quality System Requirements (QSR) – Complaint Files – 21 C.F.R. § 820.198	• Establishment Registration and Device Listing - 21 C.F.R. § 807 • Labeling Requirements – 21 C.F.R. § 809.10 (including UDI, Part 801, subpart B) • Investigational Requirements – 21 C.F.R. § 812	Quality System Requirements (21 C.F.R. Part 820) • design controls under § 820.30; • purchasing controls (including supplier controls) under § 820.50; • acceptance activities (receiving, in - process, and finished device acceptance) under §§ 820.80 and 820.86; • CAPA under § 820.100; and • records requirements under § 820, subpart M	• Premarket Review for High Risk IVDs (PMAs)	• Premarket Review for Moderate and Low Risk IVDs (510(k) and De Novo) **Most Low Risk IVDs are exempt from premarket review

Targeted Enforcement Discretion

FDA intends to continue exercising *general* enforcement discretion with respect to a limited number of categories of LDTS:

- **"1976-Type LDTs**" (exhibiting certain characteristics common among LDTs offered in 1976, characterized by manual techniques performed by laboratory personnel, using components legally marketed for clinical use)
- **Human Leukocyte Antigen (HLA) LDTs** used in connection with transplantation
- **LDTs intended solely for forensic purposes** (*i.e.*, law enforcement)
- **LDTs manufactured and performed within the Department of Defense (DoD) and Veterans Health Administration (VHA)**
- **Public Health Surveillance Tests**

Targeted Enforcement Discretion (Cont.)

FDA intends to exercise enforcement discretion ***with respect to premarket review requirements only*** for:

- **LDTs approved under New York State Department of Health's Clinical Laboratory Evaluation Program (NYS CLEP)**
- **Certain modified versions of another manufacturer's 510(k) cleared or De Novo authorized test**

- However, FDA expects compliance with other requirements described in the phaseout policy

Targeted Enforcement Discretion (Cont.)

FDA intends to exercise enforcement discretion ***with respect to premarket review requirements and most quality system requirements*** *(except for requirements under 21 C.F.R. Part 820, subpart M (Records))* for:

- **LDTs manufactured and performed by a laboratory integrated within a health care system to meet an unmet need of patients receiving care within the same health care system**
- **Currently marketed IVDs offered as LDTs (if they are not modified after the date of issuance of FDA's Final Rule - May 6, 2024)**
  - *Modifications that change the indications for use, operating principles, or performance specifications will require compliance with premarket review and QS requirements*
- **Certain non-molecular antisera LDTs for rare red blood cell (RBC) antigens for transfusion compatibility (when such tests are manufactured and performed by blood establishments)**
  - *FDA expects compliance with other requirements described in the phaseout policy (such as, medical device reporting, labeling, and specific quality system records requirements)*

Hospitals & Health Systems – Targeted Enforcement Discretion

- LDTs manufactured and performed by a laboratory integrated within a health care system to meet an **unmet need of patients receiving care within the same health care system are exempt *with respect to premarket review requirements and most quality system requirements.***

Hospitals & Health Systems – Targeted Enforcement Discretion (Cont.)

- Concern that laboratories integrated within a health care system would be more likely to stop developing LDTs for unmet needs due to cost of complying with premarket review and QS requirements
- Presence of risk mitigation factors that address risk of harm from inaccurate or unreliable LDTs, such as:
  - Laboratory shares responsibility and liability with treating physicians
  - Increased communication between laboratory and treating physicians regarding the limitations, safety, and effectiveness of LDTs
  - Input from ordering physicians may help laboratories make necessary adjustments, improvements, and other changes to the LDT

Hospitals & Health Systems – Targeted Enforcement Discretion (Cont.)

Limitations:

(1) LDTs must be **ordered by a health care practitioner on the staff or with credentials and privileges at a facility owned** and operated by the **same health care system employing the laboratory director and performing the LDT**

(2) Does not include patients being treated at an affiliated hospital with a separate corporate structure from the laboratory

Hospitals & Health Systems – Targeted Enforcement Discretion (Cont.)

(3) LDTs must address an **unmet need**

- FDA considers an LDT to be for an unmet need where there is no available FDA-authorized IVD that meets the patient's needs. This may be because:
  - (A) There is no FDA-authorized IVD for the disease or condition
  - (B) There is an FDA-authorized IVD for the disease or condition, but it is not indicated for use on the patient
  - (C) There is an FDA-authorized IVD, but it is not available to the patient
- FDA does *not* consider an LDT to be for an unmet need when it merely offers potential improvements in performance or lower cost in comparison to an FDA-authorized IVD
- An LDT would no longer fall under this enforcement discretion policy once an IVD is subsequently FDA-authorized
  - Laboratories will be expected to monitor and may be required to submit a premarket authorization at that time

Hospitals & Health Systems – Targeted Enforcement Discretion (Cont.)

(4) Laboratories integrated within health care systems **must still comply with registration, listing, and adverse event reporting requirements**.

- Although health care systems may already have mechanisms for reporting and tracking adverse events, FDA argues centralized reporting enables FDA to track trends across devices of the same type, identify when issues arise, and work with stakeholders to address those issues.

Hospitals & Health Systems – Targeted Enforcement Discretion (Cont.)

- **Unmet Need Examples:**
  - An LDT that is intended for cytogenetic analysis . . . . associated with rare diseases or conditions, certain metals testing, vital load monitoring for some transplanted-associated viruses, or diagnosis of certain mosquito-and tick-borne-diseases, *where there is no FDA-authorized IVD for the disease or condition*
  - An LDT to accommodate an alternative specimen type that is infrequently tested when the specimen type required for the FDA-authorized IVD *is not and cannot be made available*
  - An LDT for use on pediatric patients when FDA-authorized IVDs are indicated for use on adults only
  - An LDT that generates results in a significantly shorter period (e.g., hours versus days) than an FDA-authorized IVD with the same indication where due to the circumstances of the patient, the shorter time period to get results is critical for the clinical decision being made
  - An LDT for the same indication as an FDA-authorized IVD that is offered only in another health care system that is not accessible to the patient and the developing laboratory will not make the IVD available outside its system
  - An LDT for an emerging pathogen for which there is no FDA-authorized IVD and for which FDA has not identified an emergent situation

Hospitals & Health Systems – Targeted Enforcement Discretion (Cont.)

- FDA believes this limited enforcement discretion policy will help reduce the overall impact of the phaseout policy on patient access to clinical tests, especially in rural, underserved, and vulnerable populations.
- The policy is intended to be targeted and is not intended to serve as an alternative “pathway” to market for LDTs for unmet needs.
- FDA intends to provide additional guidance on how to interpret this policy.

ACLA's Challenge to the Final Rule

- American Clinical Laboratory Association (ACLA) and a private laboratory member, HealthTrackRx, filed a lawsuit against FDA **on May 29, 2024.**
  - Challenges FDA's authority to regulate LDTs as medical devices (argues LDTs are federally regulated by CMS under CLIA) as these test are not physical products
  - Accuses the FDA of regulatory overreach, in violation of the Administrative Procedure Act
  - Seeks to have FDA's Final Rule vacated

"The medical device framework is inappropriate and ill-suited for regulating laboratory-developed tests, which are services provided by trained professionals rather than manufactured products."

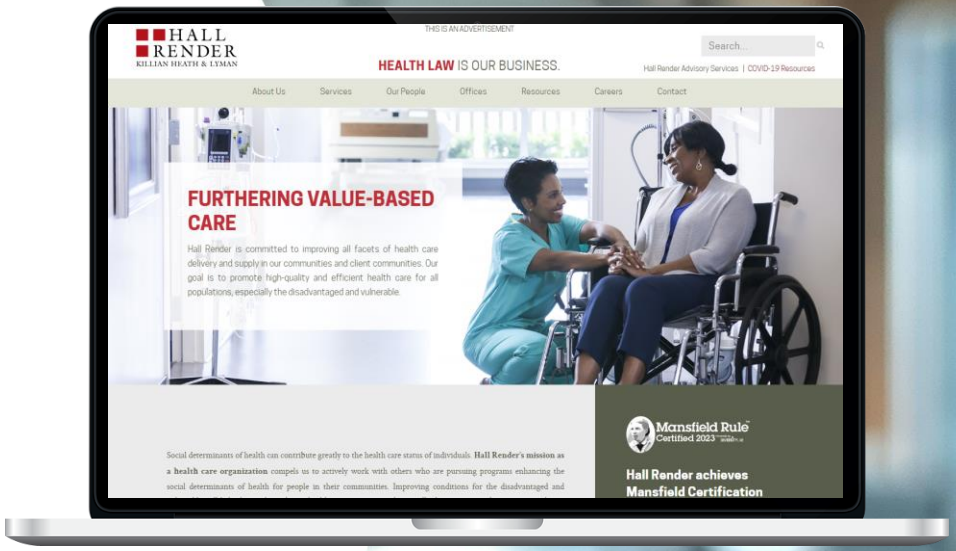
- ACLA President Susan Van Meter

Practical Takeaways

- Fate of FDA's Final Rule is still uncertain
- Prepare for enhanced oversight
- Review and update internal processes and procedures
- Consider and document products

Questions?

For more information on these topics visit hallrender.com.



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HALL RENDER
KILLIAN HEATH & LYMAN

Thank you!

Carolina M. Wirth
Shareholder
cwirth@hallrender.com
(202) 780-2989

Melissa L. Markey
Shareholder
mmarkey@hallrender.com
(248) 740-7505