U.S. FOOD & DRUG ADMINISTRATION

Welcome To Today's Webinar

Thanks for joining us!
We'll get started in a few minutes

Today's Topic:
FDA's Proposed Rule Regarding Laboratory Developed Tests

Date:
October 31, 2023

FDA's Proposed Rule Regarding Laboratory Developed Tests

Elizabeth Hillebrenner
Associate Director for Scientific and Regulatory Programs
Office of the Center Director

Center for Devices and Radiological Health
U.S. Food and Drug Administration

Proposed Rule

- FDA's Proposed Rule is aimed at helping to ensure safety and effectiveness of Laboratory Developed Tests
- Medical Devices; Laboratory Developed Tests
  - https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests

Role of Tests in Healthcare

- Diagnostic testing is a cornerstone of modern medicine; CDC estimates that 70 percent of medical decisions are based on laboratory test results

- Given the role these IVDs play in modern medical care, their validity has a significant impact on the public health.
  - False positive test results can delay diagnosis and treatment of the true disease or condition, lead to unwarranted interventions, and cause needless distress. Interventions may involve medication with serious side effects or risky medical procedures.
  - False negative results can lead to progression of disease, in some cases without the opportunity for life-saving treatment, and the spread of infectious disease.
  - The harms to patients from false positive and negative results can be significant.

Laboratory Developed Tests (LDTs)

- FDA has traditionally considered an LDT to be **an IVD** that is **intended for clinical use** and that is **designed, manufactured, and used** within **a single CLIA-certified laboratory** that **meets the regulatory requirements** under CLIA to perform high complexity testing.

- IVDs, including LDTs, are devices under section 201(h)(1) of the FD&C Act

- In implementing the Medical Device Amendments of 1976, the FDA adopted a general enforcement discretion approach for LDTs such that it generally has not enforced applicable regulatory requirements for most LDTs.
  - At that time, LDTs were mostly manufactured in small volumes by local laboratories.
  - They were typically intended for use in diagnosing rare diseases or for other uses to meet the needs of a local patient population or were generally similar to well-characterized standard tests.
  - They also tended to employ manual techniques performed by laboratory personnel without automation and be manufactured using components legally marketed for clinical use, among other things.

Evolution of LDT Landscape

- Today, many LDTs rely on high-tech or complex instrumentation and software to generate results and clinical interpretations.

- They are often used in laboratories outside of the patient's healthcare setting and are often manufactured in high volume for large and diverse populations.

- Many LDTs are manufactured by laboratory corporations that market the tests nationwide, as they accept specimens from patients across the country and run their LDTs in very large volumes in a single laboratory.

- Today's LDTs are also more commonly manufactured with instruments or other components not legally marketed for clinical use and are more often used to inform or direct critical treatment decisions, to widely screen for common diseases, to predict personal risk of developing certain diseases, and to diagnose serious medical conditions such as cancer and heart disease.

Need for the Rule

- Many test systems made by laboratories today are functionally the same as those made by other manufacturers of IVDs

- IVDs offered as LDTs have a significant impact on modern medical care
  - IVDs offered as LDTs are a growing sector of the diagnostic testing market.
  - Moreover, these tests are proliferating in some of the most complicated and sensitive areas of medical practice, where the presence of a valid test can be most important.
  - Sometimes, they use complex algorithms to calculate "scores" for diagnosis with little transparency to the user about the basis for these algorithms.
  - Increasingly, these IVDs are intended to inform drug treatment, directing physicians to choose certain drugs based on a patient's genetic or other information.

- Current information raises serious questions about whether patients can rely on IVDs offered as LDTs
  - In 2015, the Agency published a report of 20 case studies involving inaccurate, unsafe, ineffective, or poor quality LDTs that caused or may have caused patient harm.
  - More recent evidence suggests that the situation is getting worse.
    - Scientific literature
    - Allegations of problematic tests reported to FDA
    - FDA's own experience in reviewing IVDs offered as LDTs
    - News articles
    - Class action lawsuits

The Proposed Rule

- **Change to codified:**
  - This rulemaking would amend the definition of "in vitro diagnostic products" in FDA regulations (part 809, subpart A, specifically 21 CFR § 809.3) to make clear that IVDs are devices under the FD&C Act **"including when the manufacturer of these products is a laboratory."**

- The preamble describes a proposed phaseout of FDA's general enforcement discretion approach that is designed to increase oversight

- FDA seeks public comment on the proposed amendment and the matters discussed in the preamble and the Preliminary Regulatory Impact Analysis (PRIA)

Phaseout of Enforcement Discretion Approach

	Time from publication of final phaseout policy	Phase out general enforcement discretion approach for:
Stage 1	1 year	MDR requirements and correction and removal reporting requirements
Stage 2	2 years	Requirements other than MDR, correction and removal reporting, QS, and premarket review requirements
Stage 3	3 years	QS requirements
Stage 4	3.5 years, but not before Oct 1, 2027	Premarket review requirements for high-risk IVDs
Stage 5	4 years, but not before April 1, 2028	Premarket review requirements for moderate risk and low risk IVDs (that require premarket submissions)

Categories of Tests Excluded from General Enforcement Discretion Approach

For these categories of tests, FDA has generally expected applicable requirements to be met, and we are not proposing to change that approach:

- Tests that are intended as blood **donor screening** or human cells, tissues, and cellular and tissue-based products (HCT/Ps) donor screening tests required for infectious disease testing under 21 CFR 610.40 and 1271.80(c), respectively, or for determination of blood group and Rh factors required under 21 CFR 640.5
- Tests intended for emergencies, potential emergencies, or material threats declared under **section 564** of the FD&C Act
- **Direct-to-consumer** tests intended for consumer use (without meaningful involvement by a licensed healthcare professional)

Categories of Tests Not Affected by the Phaseout Policy

- **"1976-Type LDTs":** LDTs with the following characteristics, which provide the greatest risk mitigation among the characteristics that were commonly associated with LDTs offered in 1976 -
  - 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
- **Human Leukocyte Antigen (HLA) tests:** HLA LDTs for transplantation used in histocompatibility laboratories that meet the regulatory requirements under CLIA to perform 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 test
- **Forensic Tests:** intended solely for law enforcement purposes
- **Public Health Surveillance Tests:** intended solely for use on systematically collected samples for analysis and interpretation of health data in connection with disease prevention and control, and test results are not reported to patients or their healthcare providers

FDA Seeks Comment on the Following (among other things):

- **Whether specific enforcement discretion policies would be appropriate for IVDs offered as LDTs for other public health scenarios** (i.e., beyond immediate response to emerging outbreaks).

- **IVDs offered as LDTs by academic medical centers (AMCs)**
  - What are the characteristics of AMC labs? Do these characteristics in fact distinguish them from other laboratories?
  - Should FDA continue ED for any requirements for tests made by AMC labs? If so, are there any additional considerations that should be taken into account?
  - What would be the PH rationale and evidence to support a different approach for AMCs?

- **IVDs offered as LDTs by small laboratories**
  - Is there a public health rationale to have a longer phaseout period for IVDs offered as LDTs by laboratories with annual receipts below a certain threshold (e.g., $150,000)?

FDA Seeks Comment on the Following (among other things):

- **What, if any, unintended consequences may result from the proposed phaseout policy to certain patient populations** (for example, Medicare beneficiaries, rural populations, etc.)?

- **Currently marketed IVDs offered as LDTs**
  - Is there a public health rationale for continuing enforcement discretion with respect to premarket review and some or all QS requirements, for LDTs that are being offered as of the date of issuance of this proposed rule and are not changed with respect to indications for use or performance after that date?

- **Leveraging outside programs:**
  - Should FDA continue ED for any requirements where outside programs can be leveraged?
  - What should the scope of such policy be?
  - What characteristics of and activities within such programs justify such an approach?

Resources

Cited Resource	URL
Proposed Rule Regarding LDTs	https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests
Preliminary Regulatory Impact Analysis (PRIA)	https://www.regulations.gov/document/FDA-2023-N-2177-0077
Redacted Memo of Examples of IVDs Offered as LDTs that Raise Public Health Concerns	https://www.regulations.gov/document/FDA-2023-N-2177-0076
Memo Summarizing Findings from Analysis of First 125 EUA Requests from Labs for Molecular Diagnostic COVID Tests	https://www.regulations.gov/document/FDA-2023-N-2177-0121
e-Comment Portal	https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests#open-comment

A Note about the Proposed Rule

- Please submit comments on the proposed rule before closure date
  - ➢ The comment period is 60 days
  - ➢ Either electronic or written comments on the proposed rule must be submitted by December 4, 2023

Summary

- The FDA is concerned that patients could initiate unnecessary treatment or delay or forego proper treatment altogether based on inaccurate test results, which could result in harm, including worsening illness or death.
- The proposed rule is aimed at helping to ensure the safety and effectiveness of LDTs.
- The proposed rule seeks to amend the FDA's regulations to make explicit that IVDs are devices under the Federal Food, Drug, and Cosmetic Act, including when the manufacturer of the IVD is a laboratory.
- Along with this amendment, the FDA is proposing a policy under which the FDA intends to provide greater oversight of LDTs, through a phaseout of its general enforcement discretion approach to LDTs.
- The FDA believes this rulemaking would also advance responsible innovation by both laboratory and non-laboratory IVD manufacturers alike by better assuring the safety and effectiveness of IVDs offered as LDTs and removing a disincentive for non-laboratory manufacturers to develop novel tests.
- The agency's economic analysis shows that the benefits would generally outweigh the costs of the proposed rule.
- The FDA believes that all patients deserve to have access to safe and effective tests regardless of where those tests are made. This proposed rule is an important step to help ensure that healthcare decisions are made based on test results patients can trust.


FDA
U.S. FOOD & DRUG
ADMINISTRATION