FDA Proposed Rule on LDTs

Sarah McManus, MSc.
Director, Global Regulatory Affairs Diagnostics
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Drouville, *In the fish tank*

Drouville is a patient, graphic designer and artist from Argentina who has survived multiple myeloma and a relapse.

Agenda

- Overview of the Proposed Rule
- Definition of LDT
- FDA’s Reasons for the Proposed Rule
- Timelines
- Scope
- Next Steps

FDA Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 809

[Docket No. FDA-2023-N-2177]

RIN 0910-AI85

Medical Devices; Laboratory Developed Tests

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

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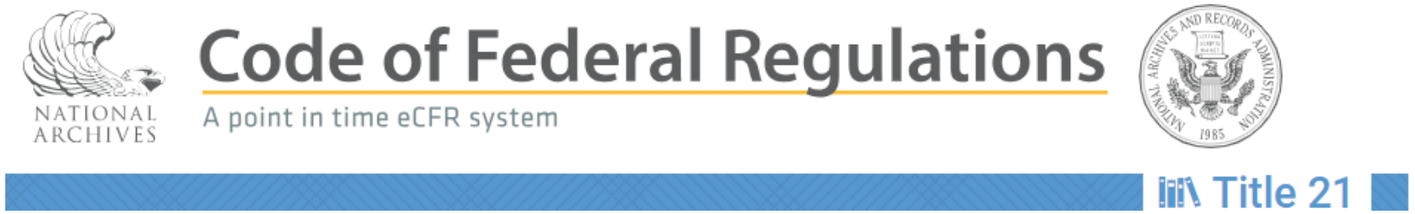
https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests

FDA Proposed Rule



PART 809—IN VITRO DIAGNOSTIC PRODUCTS FOR HUMAN USE

Authority: 21 U.S.C. 331, 351, 352, 355, 360b, 360c, 360d, 360h, 360i, 360j, 371, 372, 374, 381.

Subpart A—General Provisions

§ 809.3 Definitions.

(a) *In vitro diagnostic products* are those 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.

(b) A *product class* is all those products intended for use for a particular determination or for a related group of determinations or products with common or related characteristics or those intended for common or related uses. A class may be further divided into subclasses when appropriate.

(c) [Reserved]

(d) *Act* means the Federal Food, Drug, and Cosmetic Act.

FDA proposes to:

Amend § 809.3: update the definition of "*in vitro* diagnostic products" *to make explicit that IVDs are devices under the Food Drug &Cosmetic Act <u>including when the manufacturer of the IVD is a laboratory</u>*. FDA believes:

- LDT's are devices under the FD&C Act
- The definition of 'device' in the FD&C Act does not differentiate between the entities making the device (i.e. manufacturing facility or lab).

What is a LDT?

Laboratory-Developed Test (LDT): *an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory*. A diagnostic test that is *designed or manufactured completely, or partly, outside of the laboratory that offers and uses* the test is not considered a LDT (*Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* FDA Draft Guidance, October 3, 2014).

FDA has exercised 'enforcement discretion' over LDTs, i.e. FDA generally does not enforce the FD&C Act, however FDA may choose to do so if the test:

- Is marketed directly to consumers with no HCP oversight/involvement
- Presents a public health risk
- Performance is inadequate
- Lacks appropriate data to support performance claims
- Is not a true LDT
- Etc…

FDA's Reasons for issuing the Proposed Rule

1. FDA: There is no 'sound basis' for regulating LDTs and other IVD tests differently

"…*many test systems made by laboratories today are functionally the same as those made by other manufacturers of IVDs. They involve the same materials and technologies, are intended for the same or similar purposes, are developed by and for individuals with similar expertise, and are marketed to the same patients, sometimes on a national scale*."

- LDTs are no longer simple, manual tests performed in a health care facility's laboratosry with oversight of the results by the patient's physician.
- There is not a 'level playing field' for IVD tests – different regulatory requirements exist for laboratories and IVD manufacturers.

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FDA's Reasons for issuing the Proposed Rule

2. Safety Concerns

- FDA has concerns about LDTs *"..the evidence points to fundamental uncertainty in the marketplace about whether IVDs offered as LDTs provide accurate and reliable results*."
- FDA sources of information on LDTs: scientific literature, news articles, patient advocacy publications, complaints submitted to the FDA, Q-subs, IDE's, pre-marketing submissions, and Covid EUA submissions). In FDA's opinion, the evidence shows:
  - Inadequate validation
  - Poor reproducibility
  - Lack of clinical validation to support the stated intended use
  - Poor performance

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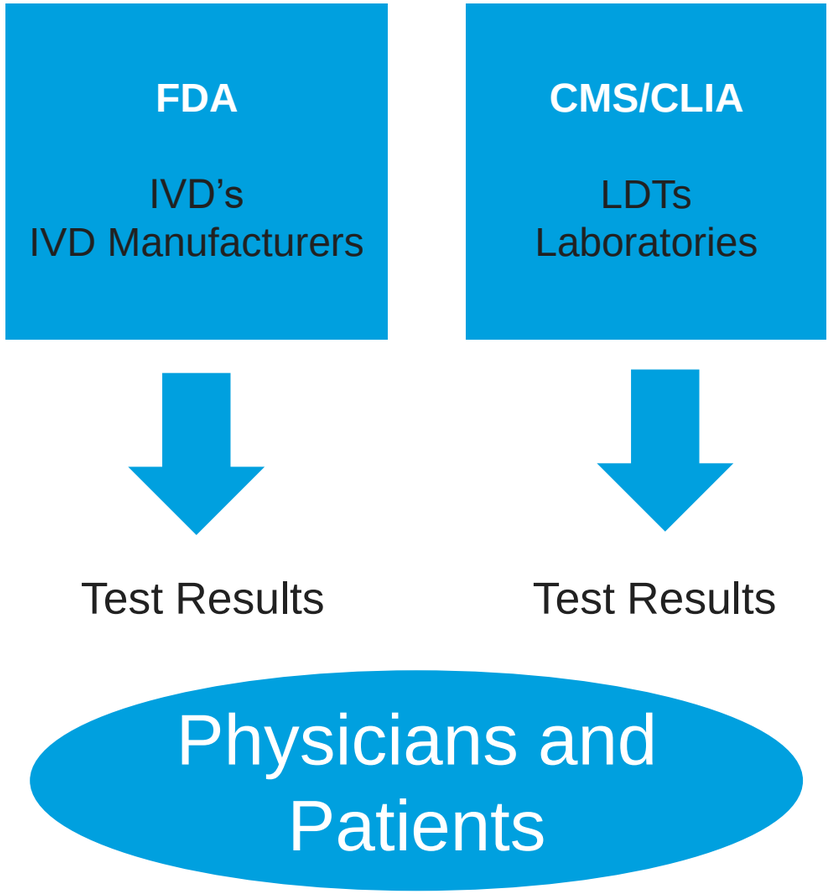
FDA's Reasons for issuing the Proposed Rule

3. To protect the public health

- Increased FDA oversight of LDTs would help to ensure the safety and effectiveness of LDTs.
- IVD's are increasingly used to identify patients likely to benefit from a therapeutic treatment and to determine the dose to administer. LDTs are now being used for these same purposes.
- 'Copy cat' LDTs create a disincentive for IVD manufacturers and may not perform as well as a similar FDA-cleared/approved IVD.
- FDA believes the public is not well served by the current 'bifurcated system' for regulating diagnostic tests.
- "CLIA is not a substitute for FDA oversight"
  - Lack of design control regulations
  - CMS does not evaluate the performance of a LDT before it is commercialized
  - CMS does not assess clinical validity
  - Lack of protection of human subjects for people who participate in clinical trials
  - No requirements for adverse event reporting



Phaseout of FDA Enforcement Discretion

FDA will increase its oversight of LDTs by **phasing out the enforcement discretion** approach to LDTs.

IVDs designed, manufactured and offered in laboratories will be subject to the same FDA regulations as IVDs offered by IVD manufacturers.

FDA will expand its oversight of LDTs from post-marketing enforcement discretion to pre-marketing authorization, general controls, AE reporting, registration & listings, etc.

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Timeline

Start	Stage 1 (+1 Year)	Stage 2 (+2 Years)	Stage 3 (+3 Years)	Stage 4 (+3.5 Years)	Stage 5 (+4 Years)
Publication of Final Phaseout Policy	•Medical Device Reporting •Correction and removal reporting	•Registration and listing •Labeling •Investigational use requirements	Compliance with Quality System Requirements (QSR)	Pre-market review of high risk IVD's.	Premarket review of moderate risk and low risk IVDs

- ❑ FDA intends to amend the QS regulation, part 820, to align more closely with international consensus standards prior to the beginning of Stage 3.
- ❑ FDA will "generally" not enforce against LDTs for which a 510(k), De Novo, or PMA request has been submitted until FDA completes its review.
- ❑ Stage 3 will start no earlier than October 1, 2027 to align with the start of fiscal year 2028, the beginning of a new user fee cycle. This will allow industry the opportunity to negotiate MDUFA VI user fees.

Products In Scope/Out of Scope

Enforcement Discretion will continue to apply (phaseout is not applicable) to:

•**1976-Type LDTs:** manual techniques performed by laboratory personnel with specialized expertise; components legally marketed for clinical use; and designed, manufactured, and used within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing (e.g. immunohistochemistry tests that involve no automated preparation or interpretation).

•**Human Leukocyte Antigen (HLA) tests** designed, manufactured, and used in a single laboratory certified under CLIA that meets the requirements 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 tests.

•Tests **intended solely for forensic** (law enforcement) purposes.

•Tests **exclusively used for public health surveillance** if: 1) intended solely for use on systematically collected samples for analysis and interpretation of health data in connection with disease prevention and control; and 2) test results are not reported to patients or their healthcare providers.

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Products In Scope/Out of Scope

Enforcement discretion was never meant to apply to:

- **Tests regulated under 21 CFR 610.40, 1271.80(c) or 21 CFR 640.5**:
  - Intended as blood donor screening or human cells, tissues, and cellular and tissue-based products,
  - Donor screening tests required for infectious disease testing
  - Tests for determination of blood group and Rh factors required under

- **Tests intended for emergencies,** potential emergencies, or material threats declared under section 564 of the FD&C Act. FDA has adopted specific enforcement discretion policies for such tests.

- **Direct to consumer tests**.

These tests must already fully comply with FDA regulations.

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Next Steps

Comments on the proposed rule are due by December 4th, 2023. FDA will then address all comments. The final rule could be published as early as Spring 2024.

FDA highlights certain topics for feedback:

- FDA asks commenters to explain the public health rationale for maintaining the general enforcement discretion approach if they believe that certain LDTs should be exempt from the phaseout.

- FDA includes a proposed definition of ‘Academic Medical center’ laboratory and asks for feedback regarding the proposed rule on AMC’s. Again, commenters are asked to justify any exemptions for AMC’s by explaining the public health rationale for doing so.

- FDA asks whether NY State CLEP or Veterans Affairs programs could be leveraged in some way.


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