The FDA Final Rule on LDTs: What You Need to Know

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FDA Final Rule

"Medical Devices: Laboratory Developed Tests"

- Publicly available on April 29, 2024
- Published in Federal Register on May 6, 2024
- "**Issuance Date**" – considered May 6, 2024
- "**Effective Date**" – July 5, 2024 (60 days after issuance date)

https://www.federalregister.gov/public-inspection/2024-08935/medical-devices-laboratory-developed-tests

Presentation Notes

1) **Slides Use Original FDA Wording as Much as is Practical**
2) **References to 4/29/24 Final Rule .pdf page #s shown at bottom right**

The Rule

Makes it explicit that IVDs are devices under the FD&C Act including when the manufacturer is a laboratory

PART 809—IN VITRO DIAGNOSTIC PRODUCTS FOR HUMAN USE

(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) (1) 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.

Definition Location[1]

Addition[2]

[1]p26; [2]p5, p25

The “Policies”

1. **Phasing out its general <u>enforcement discretion</u> approach for LDTs** so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs

2. **Adopting <u>targeted enforcement discretion</u> policies for <u>specific categories</u>** of IVDs manufactured by a laboratory

Enforcement Discretion = “we have the authority” to regulate, but *choose* not to

Concept

The FDA is claiming the power to regulate all LDTs (as IVDs)

"The phaseout policy does not in any way alter the fact that it is **illegal** to offer IVDs without complying with applicable requirements"[1]

BUT

The FDA "believe[s] an **appreciable proportion of IVDs currently offered as LDTs likely help patients** and are important to patient care…the **loss of such IVDs could cause harm** and undermine those reliance interests"[2]

SO

"It is in the best interest of public health to expect compliance with premarket review and QS requirements in a more **targeted fashion**"[3]

LDTs that specifically raise concerns

New LDTs

[1]p30, p36; [2]p61; [3]p62

Targeted Enforcement Discretion

- **“1976-type” LDTs**
- **Human leukocyte antigen (tests) for transplant**

  designed manufactured, and used within 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 law enforcement (forensic) purposes**

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Additional Enforcement Discretion

1	**Veterans Health Administration** (VHA) and **Department of Defense** (DoD)	"generally not enforce requirements"
2	LDTs approved by **NYS CLEP**	"generally not enforce premarket review requirements"
3	LDTs manufactured and performed by a laboratory integrated **within a healthcare system** to meet an **unmet need** of patients receiving care **within the same healthcare facility**	"generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)"

For QS, see p48

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Additional Enforcement Discretion

4	**Currently marketed IVDs offered as LDTs** that were first marketed prior to the date of issuance of this rule and that are **not modified**, or that are **modified in certain limited ways** as described in section V.B.3.	"generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)"
5	Non-molecular **antisera LDTs for rare red blood cell (RBC) antigens** where such tests are manufactured in blood establishments, including transfusion services and immunohematology laboratories where there is no alternative available to meet the patient's need for a compatible blood transfusion	"generally not enforce premarket review requirements and QS requirements (except for requirements under part 820, subpart M (Records)"

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Final "Phase Out" Policy

Stage	Requirements	When
Stage 1	**Medical device reporting (MDR)** requirements, **correction** and **removal** reporting requirements, and quality system (QS) requirements under § 820.198 (21 CFR 820.198) (**complaint files**)	1 year May 6, 2025
Stage 2	**Registration** and **listing** requirements**, labeling*** requirements**, and investigational use** requirements *Includes UDI, part 801, subpart B	2 years May 6, 2026
Stage 3	**QS requirements** under part 820 (21 CFR part 820) (other than requirements under § 820.198 (complaint files)	3 years May 6, 2027
Stage 4 PMAs	**Premarket review** requirements for **high-risk IVDs** offered as LDTs (IVDs that may be classified into class III or that are subject to licensure under section 351 of the Public Health Service Act), unless a premarket submission has been received by the beginning of this stage…	3.5 years Nov 6, 2027
Stage 5 510(k) and De Novo	**Premarket review** requirements for **moderate-risk** and **low-risk IVDs** offered as LDTs (that require premarket submissions), unless a premarket submission has been received by the beginning of this stage	4 years May 6, 2028

p26-27; p68-81; *p73

Requirement	Stage	Date	Pre-1976	HLA for Tx	Forensic	VHA / DoD	NYCLEP	Unmet Need	Currently Marketed	Rare RBC Antigens	New LDT	Curr. Mod.*
MDR, Correction, Removal (§ 803 and § 806)	1	May 6, 2025	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Complaint Files (§ 820.198)	1	May 6, 2025	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Registration (§ 807)	2	May 6, 2026	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Listing (§ 807)	2	May 6, 2026	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Labeling (§ 809.10)	2	May 6, 2026	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Investig. Device (§ 812)	2	May 6, 2026	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Design Controls (§ 820.30)	3	May 6, 2027	No	No	No	No	Yes	No	No	No	Yes	Yes
Purchasing Controls (including supplier controls) (§ 820.50)	3	May 6, 2027	No	No	No	No	Yes (see p48)	No	No	No	Yes	Yes
Acceptance Activities (receiving, in-process, and finished device acceptance) (§ 820.80 and § 820.86)	3	May 6, 2027	No	No	No	No	Yes (see p48)	No	No	No	Yes	Yes
CAPA (§ 820.100)	3	May 6, 2027	No	No	No	No	Yes (see p48)	No	No	No	Yes	Yes
Records (part 820, subpart M)	3	May 6, 2027 (and see p74)	No	No	No	No	Yes (store now)	Yes (store now)	Yes (store now)	Yes (store now)	Yes	Yes
Premarket Review (high-risk); PMA	4	Nov 6, 2027	No	No	No	No	No	No	No	No	Yes	Yes
Premarket Review (mod / low-risk); 510k & De Novo	5	May 6, 2028	No	No	No	No	No	No	No	No	Yes	Yes

Unmet Needs

LDTs manufactured and performed by a laboratory integrated **within a healthcare system** to meet an **unmet need** of patients receiving care **within the same healthcare facility**[1]

Limitations

- FDA does not consider this to include patients that are being treated at an **affiliated hospital** with a **different corporate ownership** than the laboratory[2]
- Policy is limited to LDTs that are **ordered by a healthcare practitioner on the staff or with credentials and privileges** at a facility owned and operated by the **same healthcare system employing the laboratory director** and performing the LDT[2]

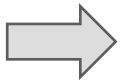
Unmet Need = When there is no available FDA-authorized IVD that meets the patient's needs.

- There is **no FDA-authorized IVD for the disease or condition** (for example, because it is for a rare 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, *or*
- There is an FDA-authorized IVD but it is **not available** to the patient[3]

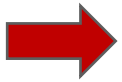
[1]p28; [2]p54; [3]p55

Unmet Need Examples

1. LDT intended for **cytogenetic analysis**…associated with **rare diseases or conditions**, certain **metals testing**, **viral load monitoring** for some **transplant-associated viruses**, or diagnosis of certain **mosquito- and tick-borne diseases**, where there is no FDA-authorized IVD for that disease or condition
2. 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
3. An LDT for use on **pediatric patients** when FDA-authorized IVDs are indicated for use on adults only
4. An LDT for the same indication as an FDA-authorized IVD that is offered only in another healthcare system that is **not accessible to the patient and the developing laboratory will not make the IVD available** outside its system
5. An LDT for an **emerging pathogen** for which there is no FDA-authorized IVD and for which the FDA has not identified an emergent situation



"potential **improvements in performance** or **lower cost** in comparison to an FDA-authorized IVD that meets the patient's needs does NOT fall within this policy"



"[When] FDA authorizes an IVD that meets the needs of the patient, then the LDT would **no longer** fall within this enforcement discretion policy"

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LDTs Currently on the Market

Currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are **not modified**, or that are **modified in certain limited ways** as described in section V.B.3.[1]

- FDA intends to request submission of the **labeling** for currently marketed IVDs as LDTs under § 807.26(e) and to use this information…to identify and address…LDTs that specifically raise concerns[2]
- **Labeling** includes **IVD performance information** and **summary of supporting validation**, as applicable[3]
- As part of its review of labeling, FDA also intends to look closely at **claims of superior performance** and whether those claims are adequately substantiated[3]
- FDA intends to enforce **records requirements** in part 820, subpart M, for **manufacturing activities** related to a currently marketed IVD offered as an LDT **that occur after the date of issuance** of this final rule[4]
- FDA expects laboratories to comply with applicable requirements other than premarket review and most QS requirements, including **MDR requirements**, **corrections** and **removals** reporting requirements, **registration** and **listing** requirements, and **labeling** requirements[4]

[1]p29;
[2]p59;
[3]p64;
[4]p65

LDTs Currently on the Market - Modifications

FDA expects compliance with **premarket review** and **QS requirements** for currently marketed IVDs offered as LDTs when a laboratory's modifications:[1,2]

- Change the **indications for use** of the IVD
- Alter the **operating principle** of the IVD (e.g., changes in critical reaction components)
- Include significantly **different technology** in the IVD

  Examples
  - addition of AI/ML
  - change from targeted sequencing to WGS
  - change from immunoassay to MS
  - change from manual to automated
- **Adversely change the performance or safety** specifications of the IVD

[1]p29; [2]p63

Modifications of Other Manufacturer's Test

- FDA is adopting a policy under which it generally does not intend to enforce **premarket review requirements** for certain laboratory changes to **another manufacturer's lawfully marketed test**[1]
  - When a **high complexity laboratory** certified under CLIA modified another manufacturer's **510(k) cleared** or **de novo** authorized test, following **design controls** and other quality system requirements described in section V.C.3, in a manner that could not significantly affect the safety or effectiveness of the test and **does not constitute a major change** or **modification in intended use**
  - FDA **would expect premarket submissions**…for the same types of changes that it would expect a premarket submission from the original manufacturer making changes to its own IVD

Policy does not apply to PMAs!

See § 807.81(a)(3) and "Deciding When to Submit a 510(k) for a Change to An Existing Device"

[1]p77-78
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device

1976-Type LDTs

- Such tests have the following characteristics:[1]
  - Use of **manual** techniques (**without automation** [and **without the use of software**][2]) performed by laboratory personnel with specialized expertise
  - Use of **components legally marketed for clinical use**
  - Design, manufacture, and use within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing

Examples

- **Immunohistochemistry** tests that involve no automated preparation or interpretation[1]
- Would **NOT** include lateral flow tests, as they do not generally rely on laboratory personnel expertise[1]
- Various tests that use **staining antibodies** and **general purpose** reagents for **cytology**, **hematology**, and **bacterial infections**[2]

- Cystic fibrosis **sweat tests**[2]
- Certain **colorimetric newborn screening tests**[2]
- Certain **immunohistochemistry tests**[2]
- **Karyotypic** tests[2]
- **Fluorescence in situ hybridization [FISH]** [2]

"FDA intends to consider whether guidance containing additional discussion and examples of tests that may fall within this category would be helpful…"

[1]p37; [2]p402

QS Requirements

- FDA recent rule amending QSRs takes effect Feb 2, 2026
- Better aligns with **ISO 13485**
- When a laboratory undertakes to comply with QS requirements, FDA will expect compliance with the QS requirements that are in effect at that time
- QS requirements applicable to CLIA lab LDTs include:

Stage 3
- **design controls** (§ 820.30)
- **purchasing controls** (including supplier controls) (§ 820.50)
- **acceptance activities** (receiving, in-process, and finished device acceptance) (§ 820.80 and § 820.86)
- **CAPA** (§ 820.100)

Stage 1
- **records** requirements under part 820, subpart M

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Immediate Public Health Response

Draft Guidance

[1]Docket No. FDA-2024-D-0083

Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564[1]

- FDA does not intend to object to the offering of **"immediate" response tests**, as defined in this guidance, when the test is manufactured and offered by **certain laboratory manufacturers**, the test has been appropriately **validated**, **FDA is notified**, appropriate **transparency** is provided, the test is **labeled for prescription use only**, and there is **no applicable 564 declaration**

> (1) intended to detect or diagnose a serious or life-threatening disease or condition that may be attributed to a newly identified, previously unknown, or unusual CBRN agent or agents; or a known agent or agents that results in a newly identified or unusual clinical presentation of such a disease or condition; and
> (2) needed for immediate response to a potential case or cases of such disease or condition for which there is no adequate, authorized, and available alternative[1]

Limited to certain tests and certain laboratories, such as those that are U.S. Government (USG) laboratories, State or local public health laboratories, or other laboratories that have agreements with the U.S.G.[1]

[1]p35

Questions on the Final Rule

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For updated ARUP FDA LDT-related information go to:

aruplab.com/fda-ldt

ARUP LABORATORIES

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