The FDA's Rule on LDTs – What it Means for You

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ADLM Association for Diagnostics & Laboratory Medicine™
Formerly AACC

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The Intent and Scope of the Rule: Key Aspects you Need to Know

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How We Got Here: A Brief Synopsis

Over the past two decades, FDA has periodically indicated a desire to exercise more regulatory oversight over laboratory-developed tests (LDTs)

Proposed oversight (with carve-outs) in mid-2010s

2021-22: VALID Act

- Congress failed to pass legislation that would give the FDA explicit oversight over LDTs

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How We Got Here: A Brief Synopsis

October 2023: FDA releases draft rule

- 4-year phase-in
- IVD = LDT
- No risk-based framework
- No technology certification
  - Exempted “traditional” LDTs, which are non-automated and use approved reagents
- Any change to indication (on the package insert) makes you a remanufacturer

60-day comment period

- >6000 comments published on FDA web site

Final Rule released officially published May 6, 2024

FDA Final Rule

- Released to the public on Monday, April 29, 2024
  - 528 pp.
- Published in the Federal Register one week later: May 6, 2024
  - This is the “official” publication date
  - Remember this date
- Officially goes into effect 60 days after publication
- Staged implementation over 4 years
  - However, all milestones are tagged to May 6 publication date

Principles of the FDA's Position

FDA asserts that they have had regulatory authority over LDTs since 1976

With respect to assays, there is no difference between an academic lab, a commercial reference lab, and an IVD manufacturer

Therefore, with minor exceptions, FDA expects an academic medical center laboratory or commercial reference laboratory to fulfill the **same** regulatory requirements as any commercial IVD manufacturer that sells kits to laboratories

A Few (Informal) Definitions, Part 1

- **Enforcement Discretion**: FDA's term which reflects their position that they have authority over LDTs but have chosen (at their discretion) to not enforce this regulatory authority. The Final Rule basically says that, moving forward, the FDA is eliminating enforcement discretion from LDTs.
  - Note that a strict reading of this and other language in the final rule implies—in the view of the FDA—labs who run LDTs have been in violation of the law since 1976

- **21 CFR 820**: The section of the code of Federal regulations that covers FDA quality systems ("QSR")
  - laboratories currently operate under 42 CFR 493, which covers CLIA

A Few (Informal) Definitions, Part 2

- **Class I/II/III**: FDA classification that refers to the level of control (Class III = the most) that is required in order to ensure safety and efficacy. Class determination is through a 513(g).
- **Premarket Review:** FDA review and approval that is required prior to deployment of an assay.

Class	Approval	User fee (FDA)	Estimated total cost (FDA)
Class III	PMA	$485,560	$4.5 million
Class I, II	De Novo reclassification	$145,068	
Class I, II	510(k)	$21,760	$250,000

Who Is Affected?

- **All** laboratories that perform laboratory-developed tests

  - **New** tests that have been developed, validated, and performed within a CLIA high-complexity laboratory
  - **Modifications** to existing FDA-cleared or approved tests, including changes to the indication
  - Covers Anatomic Pathology as well as Clinical Pathology

Who is NOT Affected?

- Labs that **only** run FDA-cleared and approved assays
  - No changes to the indication on the package insert, no alterations (e.g. no body fluids beyond those listed)
- Labs that only run "**1976-Type LDTs**"
  - Manual; no automation (e.g. no automated staining for immunohistochemistry)
  - Use only reagents that are marketed for clinical use (no RUO reagents)
  - Design/manufacture/use in a high-complexity CLIA lab
- Labs performing **HLA testing for transplant** (only applies to those assays)
- **DoD/VHA labs**, when treating patients tested and treated within the DoD or VA system.

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Are There Any Other Exceptions?

- Continued partial enforcement discretion
  - **Currently Marketed (as of May 6, 2024)**
    - **AKA "Grandfathered"**
  - **Unmet Need**
  - Rare RBC antigens
  - (NYCLEP)
- [The FDA reserves the right to exercise enforcement at any point]

What We Know: “Currently Marketed”

- Laboratory-developed tests that are “marketed” as of May 6, 2024

- After that point, these tests can be modified only in limited ways
  - Cannot change **indication** for use
  - Cannot alter the “**operating principle**”
  - Cannot include **different technology**
    - No change in **automation**
    - No addition of **AI**
    - No change in **type** of technology
  - Cannot adversely change the **performance or safety** specifications

- Changes result in a loss of the “currently marketed” status and require full FDA submission and approval

What We Don’t Know: “Currently Marketed”

- What will “count” as a significant change?
  - New Instrument?
  - Different Instrument in the same class?
  - Different Instrument in a related class?

- If a change in the “indication” removes this status, how will FDA determine the approved indications for these tests?
  - Clinical validity used to fulfill, e.g., a CAP checklist item?
    - Will not cover all labs, since clinical validity is not currently a CLIA requirement
  - Review of clinical validity data?

What We Know: “Unmet Need”

- 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 system** [emphasis mine]
  - Does NOT apply to regional referral networks that are not owned by the same corporate entity
  - For the unmet need category, every institution will need to independently develop their own LDT
    - Significant implications for the ongoing ability to developing testing for rare disease

- **Only** applies if there is not an FDA-authorized IVD that meets the patient’s needs
  - Turnaround time does factor into patient’s needs
  - However, superior performance and/or cost are not permitted as factors

What We Know: “Unmet Need”

- FDA examples:
  - Alternative specimen type
  - Pediatric use of FDA-authorized adult assay
  - Shorter time period, when TAT is critical to the clinical decision-making
  - Unavailable to the patient
    - Specific example: patient does not have access to healthcare system with authorized test AND that healthcare system refuses to test
  - Emerging pathogen, no emergency declaration

What We Don’t Know: “Unmet Needs”

- Does access to instrumentation affect the “availability” of an FDA-authorized assay?
  - For example: alternative sample type on automated analyzer
  - If an FDA-authorized version becomes available on another instrument, is the lab required to purchase that instrument?
  - What if two vendors have non-overlapping gaps in their authorization?

- What additional guidance will be issued?
  - Currently a major problem for the future of rare disease testing unless patients are able to travel

What Else We Don't Know: General

- For LDTs currently in development and validation (i.e. that didn't go live prior to May 6, 2024), what is required in order to meet FDA requirements? Does all validation need to be redone in an FDA framework?
- What is the nature of the validation that will be required for materials and manufacture?
  - How does this relate to traditional QC?
- What is the line (if any) between manufacture (FDA) and lab operations (CLIA)?
  - If performing the lab test is manufacturing, is a QC or PT failure subject to 21 CFR 820 tracking?
- If the laboratory is now a manufacturer, does this affect the ability of laboratorians to give prospective guidance to colleagues about the "off-label" use of a test?

The Regulatory Framework and the Decisions you Need to Make

Jonathan Genzen, MD, PhD, MBA

"Phase Out" Stages

Stage 1

1 year (May 6, 2025)

- **Medical Device Reporting**
- **Corrections and Removals**
- **Complaint files**

Stage 2

2 years (May 6, 2026)

- **Registration**
- **Listing**
- **Labeling**
- **Investigational Use**

Stage 3

3 years (May 6, 2027)

Quality System Requirements

- **Design Controls**
- **Purchasing and Supplier Controls**
- **Acceptance Activities**
- **Corrective and Preventative Actions (CAPAs)**
- **Records**

Stage 4

3.5 yrs (Nov 6, 2027)

- **Premarket Review for High Risk LDTs**

Premarket Approval

PMA

Stage 5

4 yrs (May 6, 2028)

- **Premarket Review (Low and Mod. Risk LDTs)**

Premarket Notification

510(k) and De Novo

Requirement	Stage	Date	1976 Type	HLA for Trans.	Foren.	VHA / DoD	NY CLEP	Unmet Need	Curr. Market	Rare RBC Ant.	New LDT	Minor Mod. to Curr. Mark.	Signif. Mod. to Curr. Mark.	Mod. Other's 510(k)	Mod. Other's PMA
MDR, **Correction**, **Removal** (§ 803 and § 806)	1	5/6/25	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complaint Files (§ 820.198)	1	5/6/25	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Registration (§ 807)	2	5/6/26	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Listing (§ 807)	2	5/6/26	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Labeling (§ 809.10)	2	5/6/26	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Investig. Device (§ 812)	2	5/6/26	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Design Controls (§ 820.30)	3	5/6/27	No	No	No	No	Yes	No	No	No	Yes	No?	Yes	Yes	Yes
Purchasing Controls (including supplier controls) (§ 820.50)	3	5/6/27	No	No	No	No	Yes	No	No	No	Yes	No?	Yes	Yes	Yes
Acceptance Activities (receiving, in-process, and finished device acceptance) (§ 820.80 and § 820.86)	3	5/6/27	No	No	No	No	Yes	No	No	No	Yes	No?	Yes	Yes	Yes
CAPA (§ 820.100)	3	5/6/27	No	No	No	No	Yes	No	No	No	Yes	No?	Yes	Yes	Yes
Records (part 820, subpart M)	3	5/6/27	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Premarket Review (high-risk); PMA	4	11/6/27	No	No	No	No	No	No	No	No	Yes	No	Yes	No	Yes
Premarket Review (mod / low-risk); 510(k) & De Novo	5	5/6/28	No	No	No	No	No	No	No	No	Yes	No	Yes	No	N/A (PMA)

Please send comments/edits to jonathan.genzen@aruplab.com. See Final Rule for exact requirements.

For Illustration Purposes Only

Stage 2: Labeling – Reagent Example

In Vitro Diagnostic Products

- Device name
- Intended use
- Reactive ingredients
- Required warning
- Storage instructions
- Assurance meets standards
  - Expiration date
  - Indication of alteration
  - Method to meet standards
- Net quantity of contents
- Name and place of manufacturer
- Lot or control numbers for tracing

Package Insert

- Proprietary name
- Intended use and type of product (qual vs quant)
- Summary and explanation of Test
  - Short history of methodology
  - Pertinent references
- Principles of the procedure (chemical reactions and techniques)

+ For Reagent

- Name, quantity, proportion of each reactive ingredient
- Statement of warnings and "for in vitro diagnostic use"
- Instructions for reconstitution, mixing, dilution
- Storage and stability instructions
- Statement of purification or treatment required for use
- Indications of instability or deterioration

+ Step By Step Procedure

- List of materials provided
- List of materials required but not provided
- Description of amounts of reagents necessary, times, steps
- Stability of final reaction material to be measured
- Details of calibration
- Details of kind and quality control materials

- Results (and procedures for calculations)
- Limitations
- Expected values
- Specific **performance characteristics** (as appliable, accuracy, precisions, specificity, sensitivity)
- Bibliography

For complete requirements please see:
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-809/subpart-B

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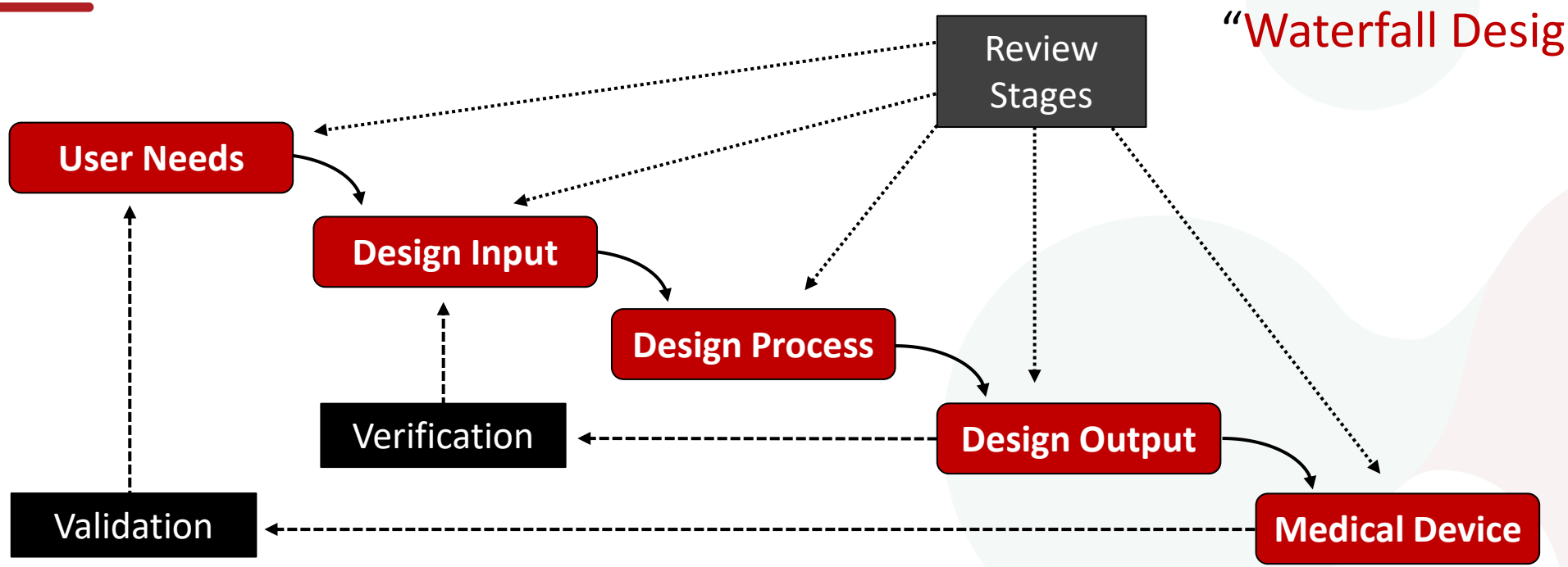
Stage 3: Design Control Example

"Waterfall Design Process"



Verification	"Did you Make the Right Product"	or	"Was the Product Built Right"
Validation	"Does the Product Work as Intended"	or	"Was the Right Product Built"

[1,2]

Figure modified from *Design Control Guidance for Medical Device Manufacturers*. FDA. March 11, 1997. Originally based on figure from Medical Devices Bureau, Health Canada. [1]https://synectic.net/verification-vs-validation-of-medical-devices/ [2]https://vantagemedtech.com/do-you-know-the-difference-between-verification-and-validation/

Predetermined Change Control Plans

(PCCPs)

A plan, proposed by a manufacturer, that specifies[1]

- certain **planned modifications** to a device
- the **protocol for implementing and controlling those modifications** and
- the **assessment for impacts** from modifications

- FDA granted authority to authorize PCCPs in 2022[2]
- 2023 Draft Guidance on PCCPs in 2023[3]
- FDA intends to issue further guidance in 2024 for use of PCCPs more broadly

Potential Applications

Multiplex / Multiple Analyte Assays

- **NGS**
- **Tox**
- **AP**

Anticipated Test Changes

Submitted as Part of **Premarket Review**

[1]https://www.fda.gov/medical-devices/software-medical-device-samd/predetermined-change-control-plans-machine-learning-enabled-medical-devices-guiding-principles;
[2]https://www.fda.gov/medical-devices/medical-devices-news-and-events/cdrh-issues-guiding-principles-predetermined-change-control-plans-machine-learning-enabled-medical;
[3]https://www.fda.gov/medical-devices/medical-devices-news-and-events/cdrh-issues-draft-guidance-predetermined-change-control-plans-artificial-intelligencemachine

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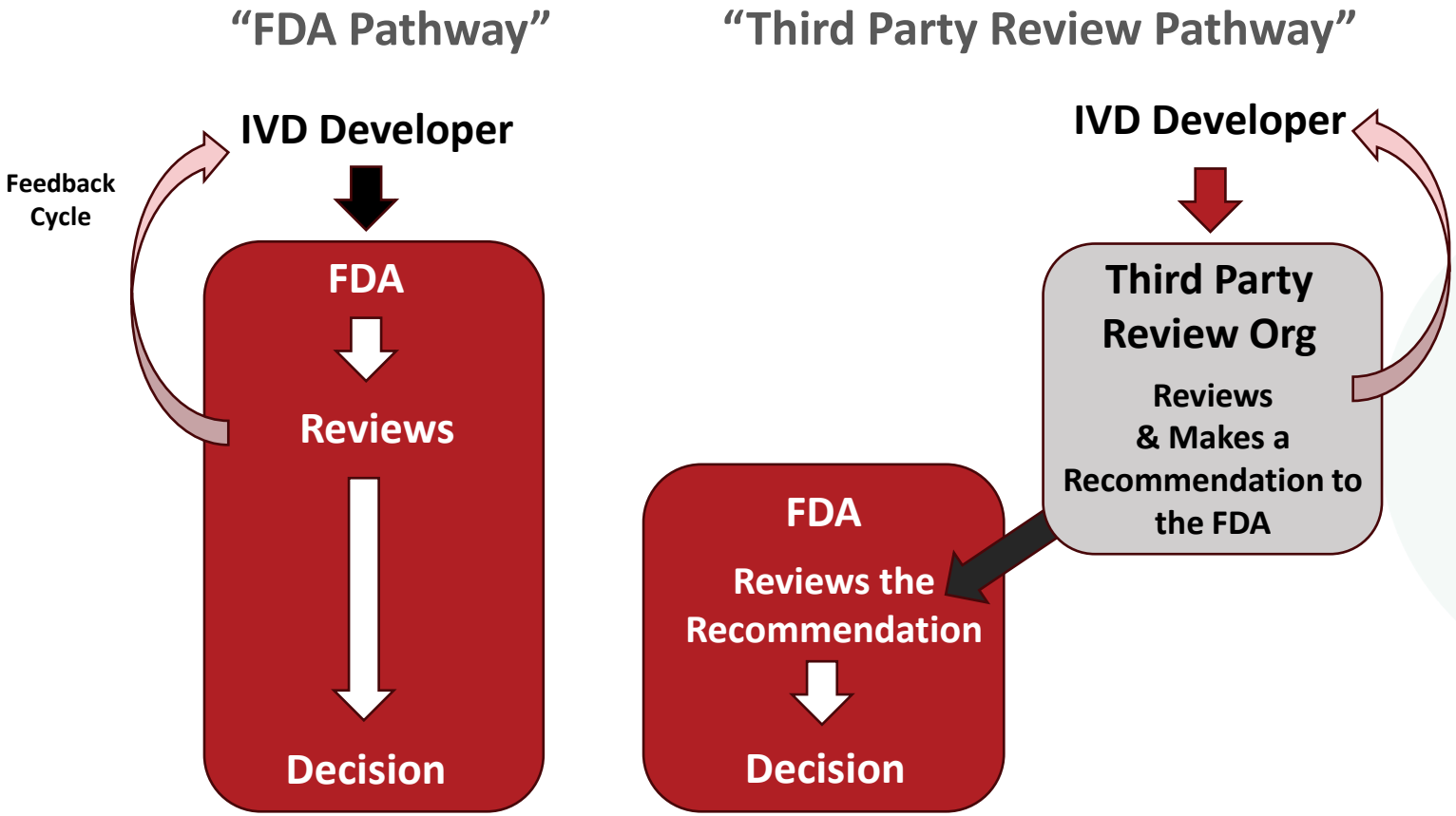
Third Party Review Program (3P510k)



- **Low and moderate risk** tests only
- Minimal use by IVD manufacturers
- Reviews limited to **eligible categories**
- **Costs** negotiated between developer and Third Party Review Organization
- Draft guidance on expansion to include **EUAs**

Figure based on *510(k) Third Party Review Program. Guidance for Industry, Food and Drug Administration Staff, and Third Party Review Organizations*. March 12, 2020.

Staffing, Resources, and Regulatory Affairs

Personnel

- **Assigning and/or hiring individuals** to meet phase out stage requirements
- **Training** and **education**

Resource Allocation

- Identifying and allocating **resources** to meet compliance costs and new requirements

Regulatory Affairs

- Developing an FDA-centric regulatory **infrastructure, team**, and **strategy**

Areas Needing Immediate Clarity

Requirements During Transition Period

- Introduction of New Tests
- Work completed prior to stage requirements vs FDA expectations at Stages 4 and 5

Discipline Specific Questions (Flow, Mass Spec, ID, Molecular)

- New Antibodies, Probes, and Targets
- Equipment
- RUO / ASRs
- Multiplex Testing

Anatomic Pathology

- Antibodies
- Automation
- Optimization
- Immediate Care
- Digital Pathology

Assay Automation

- Types
- Requirements
- Clinical and Workflow Impact

What Happens Moving Forward

Congress

Litigation

Election

Questions

Speaker Emails

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