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FDA Rule on Lab Developed Tests (LDTs) for Laboratories Setting Up Molecular LDTs

On Apr 29 2024, the FDA announced a final rule for regulating CLIA LDTs, essentially treating LDTs as IVDs (in vitro devices) that are manufactured by a single laboratory. This note summarizes the guidance and explores implications for existing and new CLIA LDTs. For those who might need assistance to assess or meet these requirements, Strand will be happy to help.

FDA LDT Guidance Summary

- An IVD (In Vitro Diagnostic) is a device under the Federal Food, Drug and Cosmetic Act (FD&C) and needs to be compliant with device requirements in the FD&C Act.
- Laboratory Developed Tests (LDTs) are IVDs intended for clinical use and are designed, manufactured and used within a single clinical laboratory certified under the Clinical Laboratory Improvements Amendments (CLIA, 1988). Thus far, the FDA has exercised "enforcement discretion" for LDTs, i.e., it has generally not required LDTs to comply with the device requirements in the FD&C Act
- However, in April 2024, the FDA announced a phaseout of the general enforcement discretion policies, citing the increased use of LDTs, by a more diverse population, and for the purpose of guiding healthcare decisions

By when?

The phaseout of enforcement discretion consists of 5 stages. Each Stage enforces a successively greater degree of compliance with the device requirements in the FD&C Act.

Stage 1	**May 6, 2025**	(compliance with) Medical device reporting (MDR) requirements, correction and removal requirements, and quality system (QS) requirements for complaint files (Note: Complaint files are process for managing complaints and taking Corrective and Preventive Action or CAPA)
Stage 2	**May 6, 2026**	Registration and listing requirements, labeling requirements, and investigational use requirements
Stage 3	**May 6, 2027**	QS requirements other than those for complaint files
Stage 4	**Nov 6, 2027**	Premarket requirements for high-risk (Class III) IVDs offered as LDTs, OR receipt of a premarket submission to the FDA prior to the start date, in which case enforcement discretion applies pending FDA review of submission.
Stage 5	**May 6, 2028**	Premarket review requirements for moderate-risk and low-risk IVDs offered as LDTs (that require premarket submissions), OR receipt of a premarket submission prior to the beginning of this stage, in which case enforcement discretion applies pending FDA review of submission.

Which LDTs?

FDA will continue to exercise enforcement discretion, i.e., not all of the rules above will be applicable to all laboratories. For clarity, the types of compliance required are divided into Tiers 0-IV in the table below, with Tier 0 listing tests for which the compliance required by the final rule is already expected and enforced.

	STAGE 1	STAGE 2	STAGE 3	STAGE 4	STAGE 5
Tier 0	✓	✓	✓	✓	✓
• Donor screening tests for infectious diseases and certain blood typing tests • Direct-to-Consumer (DTC) tests	**Stage 1-5** compliance currently expected				
Tier 1	✗	✗	✗	✗	✗
• Public health surveillance tests • 1976 type LDTs • HLA tests for transplantation • Forensic tests • LDTs manufactured within DoD and VHA	Exempt from all final rule compliance requirements (enforcement discretion continues)				
Tier 2	✓	✓	✓	✗	✗
• LDTs for unmet needs manufactured and performed by labs integrated in the healthcare system treating the patient • LDTs marketed prior to Stage 1 date and not modified or modified with limitations (so indications for use, operating principles, and technology remain the same and performance is no worse) • Non-molecular antisera LDTs for rare RBC antigens	**Stage 1** compliance required (MDR, correction and removal, and complaint file QS) **Stage 2** compliance required (registration and listing, labeling, and investigational use requirements) **Limited Stage 3** compliance required (21 CFR 820 Subpart M 180-820.186, record keeping) **Stages 4 and 5** Exempted (premarket review)				
Tier 3	✓	✓	✓	✗	✗
• LDTs with NY State CLEP approval • Modified version of another manufacturer's 510 (k) cleared or de novo authorized test	**Stage 1, Stage 2 and Stage 3** compliance required **Stages 4 and 5** Exempted				
Tier 4	✓	✓	✓	✓	✓
• LDTs that do not fall into the categories above	**Stage 1-5** compliance required				

1976-type LDTs are tests that involve use of manual techniques (without automation) performed by laboratory personnel with specialized expertise, use of 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

New Molecular LDTs

Laboratories seeking to develop, manufacture and market LDTs after the publication of the Final Rule (new LDTs) will need to determine:

a. **Exemptions** to what degree, if any, they qualify for any exemptions

b. **Systems and Processes** Based on the answer to a., what systems and process will need to accompany the LDT in order to comply with the final rule.

c. **Timeline** Based on the answer to b. and the Stages of enforcement discretion phaseout, when these systems and processes need to be put into place.

d. **Cost** Based on the answers to b, and c, the costs of setting up these processes

Is my LDT exempt? If so, to what degree?

Exempt from all requirements.

a. Your molecular test is exempt from all final rule requirements if it is an HLA test

b. Your molecular test is exempt from all final rule requirements if it's a Tier I test as in the above table. For molecular tests, the only plausible such category other than the HLA test is the 1976-type test, which requires the use of fully manual processes by laboratory personnel, the use of components legally marketed for clinical use, e.g. tests that exclusively use other IVDs marketed for clinical use, and are used within a CLIA-approved lab. Most new molecular tests will not fall under a 1976-type test category, due to its use of modern automation as well as components that may be RUO.

Exempt from premarket review requirements.

Your test is exempt from premarket review requirements if it's either a Tier 2 or 3 test in the above table. For new molecular lab tests, this generally implies a further two possibilities:

a. **LDTs for unmet needs manufactured and performed by labs integrated in the healthcare system treating the patient.** This requires fulfilling two criteria:

   i. Does my LDT fulfill an unmet need?

   ii. Will my test or can my test be integrated into the healthcare system treating the patient, i.e., a hospital or an academic medical center (AMC)?

b. **LDTs that have NY State CLEP approval.** If your lab is in the state of New York, or is otherwise seeking to market its LDT in the state of New York, it will need NY State CLEP approval. Obtaining NY State CLEP approval will further exempt your LDT from the onerous premarket approval needed in either Stage 4 for high risk or Stage 5 for medium and low-risk LDTs.

Note that LDTs under item 2a are further exempt from most quality system requirements needed by Stage 3, except record keeping and complaint file keeping requirements.

The FDA notes it anticipates that many LDTs manufactured by AMC laboratories will fall within the unmet needs policy. This has led to the recommendation that companies with new LDTs that choose to partner with AMCs might need only Tier II rather than Tier III compliance. However, unless the new LDT fulfills an unmet need, merely partnering with AMCs is unlikely to result in a lower tier of compliance. Offering the test in an AMC also has commercial implications for the LDT beyond the scope of this document.

What systems and processes do I need to set in place, and when?

Most new molecular LDT manufacturers will not be exempt and hence fall under one of the Tiers II, III, or IV.

	STAGE 1	STAGE 2	STAGE 3	STAGE 4	STAGE 5
Tier II, III	✓	✓			
Tier III	✓	✓	✓		
Tier IV	✓	✓	✓	✓ - or -	✓

- Medical device reporting
- Correction and removal
- Complaint files
- Registration and listing
- Labeling
- Investigational use
- Record keeping requirements

- Quality system requirements

- Premarket review

What will this cost?

Determining the cost of compliance for a new molecular LDT to the new LDT rule will depend on:

1. A detailed description of the LDT
2. Accompanying descriptions/documents of validation of LDT, CLIA reports, etc
3. Planned LDTs
4. Laboratory systems currently in place
5. Compliance to MDR, correction and removal, QS, labeling, Investigational Use etc currently in effect
6. Laboratory budgets by year for new systems

Depending on item 1, Strand will consult with the laboratory in a ≈2 month timeframe to determine the systems that need to be put in place for a phased compliance with Stages 1, 2 and 3 of the Final Rule. Additionally, if the test requires either Stage 4 or 5 premarket review compliance, Strand will interface with an FDA consultant to come up with a plan for such compliance, as well as timelines. Since Stage 4/5 compliance is not needed before Nov 2027, this is expected to occur well after the Stage 1-3 consultation above.

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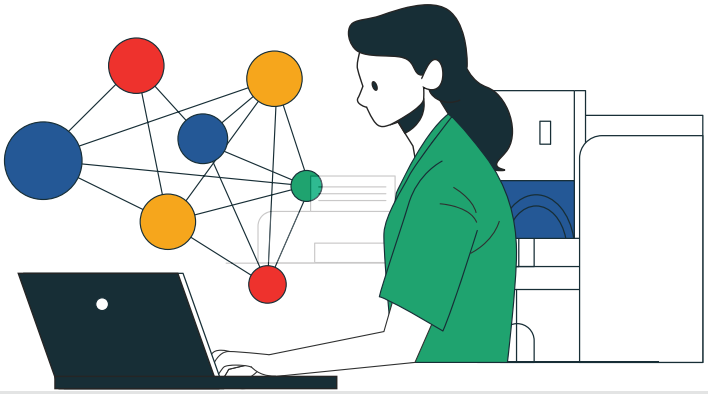
Provisos

1. The FDA's ability to regulate LDTs emerges from its classification of LDTs as a type of IVD. Both its ability to regulate and the classification are being or are soon expected to be legally contested.
2. FDA notes in the preamble to the Final Rule that it "retains discretion to pursue enforcement action at any time against violative IVDs when appropriate," regardless of enforcement discretions specified in the Final Rule.



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