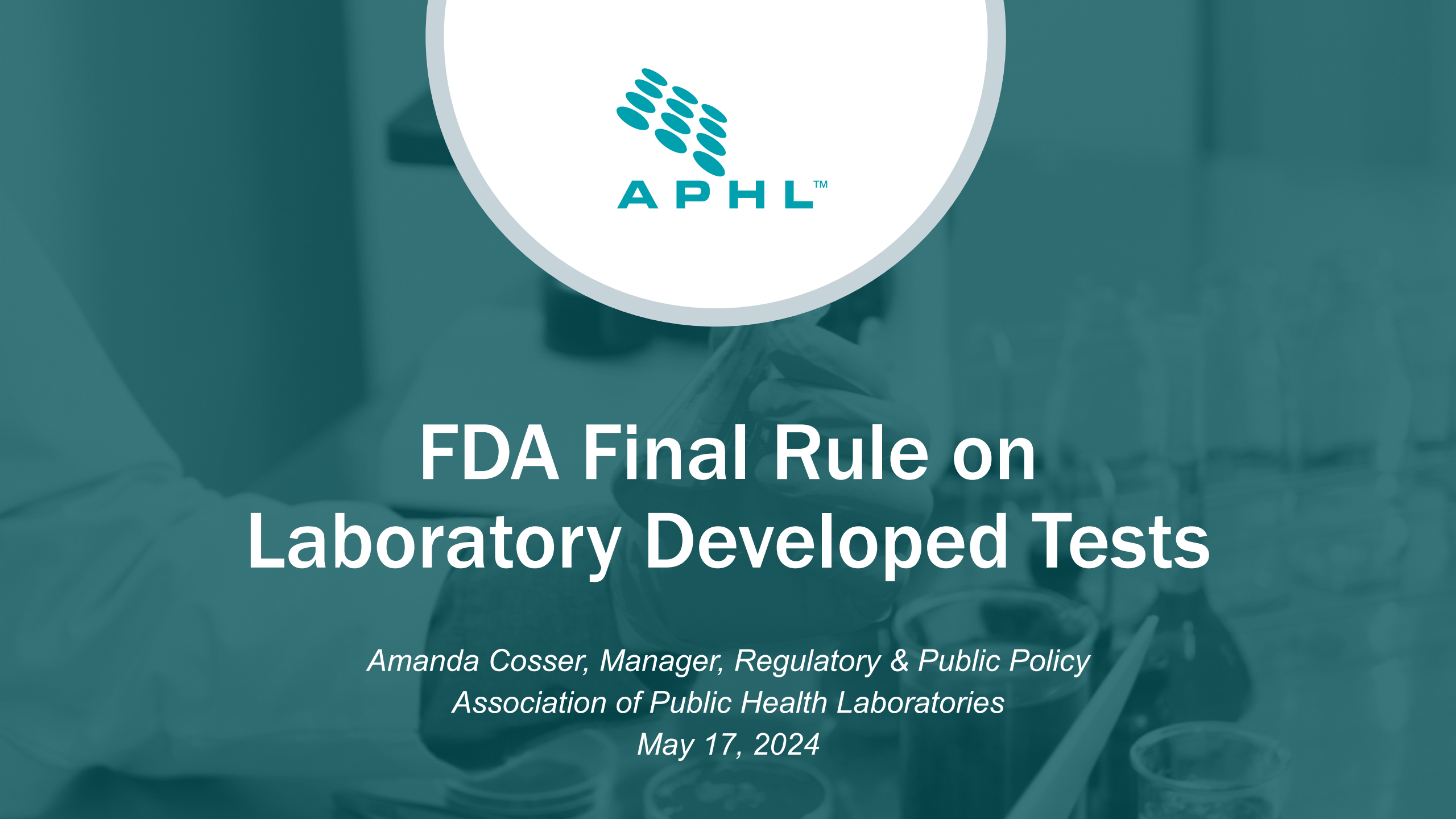

FDA Final Rule on Laboratory Developed Tests

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Association of Public Health Laboratories
May 17, 2024

APHL Feedback Gathering Process

- Webinar, meetings, calls, emails, and ColLABorate chats
- Guidance for commenting
- Many APHL members and partners commented on the proposed rule (not an all-inclusive list)

- Comment from San Francisco Department of Public Health Population Health Division
- Comment from Connecticut Department of Public Health State Public Health Laboratory
- Comment from Tennessee Public Health Laboratory
- Comment from Washington State Department of Health, Washington State Public Health Laboratories
- Comment from Oregon State Public Health Laboratory
- Comment from State of Utah Public Health Laboratory
- Comment from Texas Department of State Health Services
- Comment from Wisconsin Department of Health Services
- Comment from NYS-DOH-Wadsworth Center
- Comment from Washington State Public Health Laboratories
- Comment from Monterey County Public Health Laboratory
- Comment from Sonoma County Public Health Laboratory
- Comment from Missouri State Public Health Laboratory
- Comment from Contra Costa Public Health Laboratory
- Comment from California Department of Public Health Center for Laboratory Sciences
- Comment from County of San Luis Obispo Public Health Laboratory
- Comment from Minnesota Department of Health Laboratory
- Comment from Debbie Gibson (Montana PHL)
- Comment from Allen Bateman (WSLH)
- Comment from National Coalition of STD Directors
- Comment from WA State Department of Health (NBS Program Director)
- Comment from Big Cities Health Coalition
- Comment from Council of State and Territorial Epidemiologists (CSTE)
- Comment from National Association of County and City Health Officials
- Comment from Infectious Diseases Society of America
- Comment from American Society for Clinical Pathology
- Comment from NASTAD
- Comment from Muscular Dystrophy Association

LDT proposed rule_APHL comments

2023 LDT rule_Template for comments (aphl.org)

APHL Comments

- Agreed that FDA has a role in oversight of LDTs.
- Must consider unintended consequences that could limit access or burden the public health system.
- PHLs must continue to operate and fulfill their unique mission under the final rule.

Concerns

- PHLs have limited resources.
- Decreased or limited access to tests of public health concern (health threats and emergencies).
- LDTs are needed to meeting population, specimen type, or testing volume needs.
- LDTs are needed to test for drug resistance and determining antimicrobial susceptibility and efficacy.
- LDTs are utilized to provide more services and serve a greater population.
- Detrimental impact on surveillance and outbreak monitoring.

Recommendations

- Expand the scope of enforcement discretion:
  - For public health surveillance (results can be returned).
  - For PHL LDTs used for at least two years.
  - For PHL assays that are LDTs due to certain modifications to FDA-approved tests.
  - For public health emergencies to include assays needed for outbreaks of any size (before and during).
- Provide a less burdensome pathway for PHL LDTs.
- Stratify the phaseout period for LDTs and provide more information/guidance on submitting applications.

LDT Final Rule &
Draft Policies for Emergent Situations

Definitions

In vitro diagnostic (IVD) device: 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, and intended for use in the collection, preparation, and examination of specimens taken from the human body.

Laboratory developed test (LDT): FDA has generally considered an LDT to be an IVD that is intended for clinical use and that is designed, manufactured, and used within a single laboratory that is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and meets the regulatory requirements under CLIA to perform high complexity testing.

Summary

- IVDs are devices under the Food, Drug, & Cosmetic Act including when the manufacturer is a lab. These IVDs include LDTs.
- Effective July 5, 2024.
- Four-year, five-stage phaseout of general enforcement discretion.
- Continued enforcement discretion for:
  - 1976-Type LDTs
  - Human leukocyte antigen tests
  - Forensic (law enforcement) tests

Summary

- New – Targeted enforcement discretion for:
  - LDTs approved by New York State Clinical Laboratory Evaluation Program (**CLEP**).
  - LDTs **currently marketed** and not modified following issuance of the final rule (May 6, 2024) or only modified as described in the final rule.
  - LDTs for **unmet needs** manufactured and performed by a **lab integrated with a healthcare system** for patients receiving care at that healthcare system (hospital labs, most academic medical centers).
  - LDTs manufactured and performed within the **Veterans Health Administration or Department of Defense.**
  - Non-molecular antisera LDTs for **rare blood cell antigens** when no alternative to meet patient's need for a compatible blood transfusion.

Summary

- New – Draft policies:
  - Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564
  - Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency
  - Informational webinar June 5, 2024 at 1:00 PM ET.
  - Public comments due July 5, 2024.

Were APHL's recommendations reflected in the final rule?

APHL recommendation:
Expand enforcement discretion for public health surveillance.

Final Rule:

- Public health surveillance tests are distinct from other tests (page 34).
  - Solely for use on systematically collected samples.
  - **Results are not reported** to patients or healthcare providers.
  - The results are mostly **used for population-based trending** or **public health outbreaks** (not clinical decision-making).
- FDA believes these tests will not be affected by the enforcement discretion phaseout.
  - "**Surveillance tests are not used for individual decision-making**. Screening tests are distinct from public health surveillance tests and do fall within the phaseout policy."

APHL recommendation:

Expand enforcement discretion for PHL LDTs used for at least two years without any reported adverse consequences.

Final Rule:

- FDA intends to exercise **enforcement discretion** and generally not enforce premarket review and QS requirements (except for requirements under part 820, subpart M (Records)) **for currently marketed IVDs offered as LDTs** that are not modified or that are modified as described in section V.B.3 (including those manufactured by public health laboratories) **and** generally not enforce premarket review requirements for **LDTs approved by NYS CLEP** (including those manufactured by public health laboratories) (page 253).

- FDA intends to develop appropriately **targeted enforcement discretion policies for certain common changes to IVDs** (including those manufactured and offered by public health laboratories), such as **extension of specimen stability and certain alternative specimen types**, following good guidance practices.

APHL recommendation:

Expand enforcement discretion for PHL assays that are LDTs due to certain modifications to FDA-approved tests.

Final Rule:

- Enforcement discretion will continue for LDTs currently marketed.
- **Targeted enforcement discretion for common changes to IVDs** (only certain modifications, like specimen stability and alternative specimen types).
  - *New (May 14, 2024 FDA LDT webinar) – Additional allowable modifications include those that don't:*
    - *Change the indications for use,*
    - *Alter the operating principle of the IVD,*
    - *Include significantly different technology, or*
    - *Adversely change the performance or safety specifications of the IVD.*
  - *This includes new instruments.*
- Will review any interpretation guidance to understand impact on PHLs.

APHL recommendation:

Provide a less burdensome pathway for PHL LDT review/approval.

Final Rule:

- **Acknowledged the various unmet needs for which PHLs offer LDTs** including newborn screening for RUSP disorders without FDA-approved tests, infectious diseases, toxicology (blood lead), drugs of abuse, and rare diseases as well as compliance costs (pages 421-422).
- Enforcement discretion for **rare disease LDTs (but not those at PHLs)**—healthcare system labs. Inappropriate to extend to PHLs or labs not integrated in a healthcare system because they **lack similar risk mitigation measures**.
- **PHLs do not merit a different approach**/policy/streamlined process, so enforcement discretion for currently marketed tests and some modifications to IVDs.

APHL recommendation:

Phaseout low-risk LDTs last and provide more guidance for submitting applications.

Final Rule:

- Enforcement discretion for **low-risk LDTs will be phased out last** (during stage 5 of the four-year, five-stage phaseout policy).
- FDA intends to consider **additional resources** such as guidance documents and templates.
- *New (May 14, 2024 FDA LDT webinar) – FDA acknowledged validation challenges for low prevalence diseases.*
  - *It can be difficult to obtain specimens.*
  - *FDA intends to consider issuing additional guidance on test validation.*

APHL recommendation:

Expand enforcement discretion for public health emergencies (PHEs) to include assays needed for outbreaks of any size (before and during a PHE).

Final Rule:

- Phasing out general enforcement discretion for LDTs, **issuing guidance** with an enforcement discretion policy **for "immediate response" tests.**
- Concurrently released **two draft guidance documents** for public comment (due July 5, 2024) **for IVDs in absence of a declared PHE and during a PHE.**
  - "For immediate response to chemical, biological, radiological, or nuclear (CBRN) agents."

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

- FDA plans to **consult with CDC** regarding a potential emergent situation.
- **Many considerations**: geographic spread, ease of transmissibility, analyses of transmission potential, population at risk, morbidity/mortality rates, hospitalization/healthcare rates, availability of existing countermeasures, and any information from test manufacturers/clinical labs.
- When appropriate: **will announce when LDT final rule enforcement policy does not apply to "immediate response" tests**:
  - They detect/diagnose a newly identified or unusual CBRN or known CBRN agent presenting in a new way.
  - An immediate response is needed, and no adequate approved/cleared/authorized alternative exists.
  - They will **help with the government's coordinated public health response.**

Enforcement discretion policy (no PHE) includes:

- Tests manufactured and offered within a **single CLIA-certified high complexity US government (USG) lab, state/local PHL**, lab under agreement with USG or CDC for distribution to these labs (within CDC, **LRN**, or under an agreement with CDC) *(with demonstrated ability to develop these tests).*
- **Test appropriately validated** prior to testing and performance summary made **publicly available** *(30 pos, 30 neg, LOD, sensitivity, specificity, reactivity).*
- **FDA notified** *(email prior or concurrent with testing initiation).*
- Appropriate **transparency** *("CBRN test not reviewed or authorized by FDA").*
- Test labeled for prescription use only and **no applicable 564 declaration.**

Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency

- **GAO recommendation**: develop policy for enforcement discretion for unauthorized tests in future public health emergencies".
- Draft guidance describes FDA considerations for unapproved tests during a PHE. **FDA will assess**:
  - **Need** - Tests available, how quickly a test is needed *(Will also consider the type of test best suited for the response, including TAT collection to resulting)*
  - **Risk** - Known/potential risks *(to PH and with sample collection, certain test components)*
  - **Alternatives** - Availability of alternative authorized/approved tests to diagnose disease/condition *(will consider manufacturing capacity)*
  - **Mitigations** - Availability of sufficient mitigations to address risk of false results *(experience, participation in government evaluation program, validation recommendations, availability of confirmatory testing, public disclosure, EUA submission within a reasonable timeframe, etc.)*

Phaseout of General Enforcement Discretion (4yrs)

- **Stage 1**: Beginning 1 year after publication, must be compliant with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (21 CFR 820.198) (complaint files);
- **Stage 2**: Beginning 2 years after publication, must be compliant with requirements not covered during other stages of the phaseout policy, including registration and listing requirements, labeling requirements, and investigational use requirements;
- **Stage 3**: Beginning 3 years after publication, must be compliant with QS requirements under part 820 (21 CFR part 820) (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1);
- **Stage 4**: Beginning 3.5 years after publication, must be compliant with 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 in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review; and
- **Stage 5**: Beginning 4 years after publication, must be compliant with 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 in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review.

Reference: This text was taken directly from the final rule.

Phaseout of IVDs by Category

Please note that not all categories of IVDs are included in this table borrowed from the FDA website. Those for 564 declarations (public health emergencies) are excluded.

Reference: https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests#phaseout

Category of IVD	*Stage 1* Adverse Event Reporting (21 CFR pt. 803) Reporting of Corrections and Removals (21 CFR pt. 806) Complaint Files (21 CFR 820.198)	*Stage 2* Requirements Not Covered In Other Stages, Including: Establishment Registration & Device Listing (21 CFR pts. 607, 807 subpts. A-D) Labeling (21 CFR pts. 801, 809) Investigational Use Requirements (21 CFR pt. 812)	*Stage 3* Quality System Requirements Other than Complaint Files (21 CFR pt. 820 other than 21 CFR 820.198) (For LDTs,[1] FDA generally will not expect compliance with quality system requirements other than design controls, purchasing controls, acceptance activities, CAPA, and records requirements)	*Stages 4 & 5* Premarket Review (21 CFR pt. 807, subpt. E; 21 CFR pt. 860, subpt. D; 21 CFR 814; 21 CFR pt. 601)
Public Health Surveillance tests Section V.A.2 of preamble	compliance generally not expected	compliance generally not expected	compliance generally not expected	compliance generally not expected
Currently marketed IVDs offered as LDTs first marketed prior to rule publication date and not modified beyond scope described in preamble Section V.B.3 of preamble	compliance generally expected beginning May 6, 2025	compliance generally expected beginning May 6, 2026	compliance with 21 CFR 820.180-820.186 generally expected beginning May 6, 2027; compliance generally not expected with other QS requirements (except for complaint files)	compliance generally not expected
Modified version of another manufacturer's 510(k) cleared or De Novo authorized test within the scope described in the preamble Section V.C.4 of preamble	compliance generally expected beginning May 6, 2025	compliance generally expected beginning May 6, 2026	compliance* generally expected beginning May 6, 2027	compliance generally not expected
IVDs offered as LDTs within scope of phaseout policy, but that do not fall within a targeted enforcement discretion policy summarized above Section V.C of preamble	compliance generally expected beginning May 6, 2025	compliance generally expected beginning May 6, 2026	compliance** generally expected beginning May 6, 2027	compliance generally expected beginning November 6, 2027 for high-risk tests; compliance generally expected beginning May 6, 2028 for moderate-risk and low-risk tests

Category of IVD	*Stage 1* Adverse Event Reporting (21 CFR pt. 803) Reporting of Corrections and Removals (21 CFR pt. 806) Complaint Files (21 CFR 820.198)	*Stage 2* Requirements Not Covered In Other Stages, Including: Establishment Registration & Device Listing (21 CFR pts. 607, 807 subpts. A-D) Labeling (21 CFR pts. 801, 809) Investigational Use Requirements (21 CFR pt. 812)	*Stage 3* Quality System Requirements Other than Complaint Files (21 CFR pt. 820 other than 21 CFR 820.198) (For LDTs,[1] FDA generally will not expect compliance with quality system requirements other than design controls, purchasing controls, acceptance activities, CAPA, and records requirements)	*Stages 4 & 5* Premarket Review (21 CFR pt. 807, subpt. E; 21 CFR pt. 860, subpt. D; 21 CFR 814; 21 CFR pt. 601)
LDTs for unmet needs by labs integrated in the healthcare system treating the patient Section V.B.3 of preamble	compliance generally expected beginning May 6, 2025	compliance generally expected beginning May 6, 2026	compliance with 21 CFR 820.180-820.186 generally expected beginning May 6, 2027; compliance generally not expected with other QS requirements (except for complaint files)	compliance generally not expected
1976 type LDTs Section V.B.1 of preamble	compliance generally not expected	compliance generally not expected	compliance generally not expected	compliance generally not expected
HLA tests for transplantation Section V.B.1 of preamble	compliance generally not expected	compliance generally not expected	compliance generally not expected	compliance generally not expected
Forensic tests Section V.B.1 of preamble	compliance generally not expected	compliance generally not expected	compliance generally not expected	compliance generally not expected
DoD and VHA LDTs Section V.B.1 of preamble	compliance generally not expected	compliance generally not expected	compliance generally not expected	compliance generally not expected

Category of IVD	*Stage 1* Adverse Event Reporting (21 CFR pt. 803) Reporting of Corrections and Removals (21 CFR pt. 806) Complaint Files (21 CFR 820.198)	*Stage 2* Requirements Not Covered In Other Stages, Including: Establishment Registration & Device Listing (21 CFR pts. 607, 807 subpts. A-D) Labeling (21 CFR pts. 801, 809) Investigational Use Requirements (21 CFR pt. 812)	*Stage 3* Quality System Requirements Other than Complaint Files (21 CFR pt. 820 other than 21 CFR 820.198) (For LDTs,[1] FDA generally will not expect compliance with quality system requirements other than design controls, purchasing controls, acceptance activities, CAPA, and records requirements)	*Stages 4 & 5* Premarket Review (21 CFR pt. 807, subpt. E; 21 CFR pt. 860, subpt. D; 21 CFR 814; 21 CFR pt. 601)
Donor screening tests for infectious diseases and certain blood typing tests Section V.A.2.a of preamble	compliance currently expected	compliance currently expected	compliance currently expected	compliance currently expected
Direct-to-Consumer (DTC) tests Section V.A.2.c of preamble	compliance currently expected	compliance currently expected	compliance currently expected	compliance currently expected
Nonmolecular antisera LDTs for rare red blood cell antigens Section V.B.3 of preamble	compliance generally expected beginning May 6, 2025	compliance generally expected beginning May 6, 2026	compliance with 21 CFR 820.180-820.186 generally expected beginning May 6, 2027; compliance generally not expected with other QS requirements (except for complaint files)	compliance generally not expected

Next Steps: Final Rule Communication and Commenting

- Lab Director ColLABorate posts
- eUpdate
- Feedback requested
- Communication with partner organizations and federal agencies
- Summary document
- Other communications as appropriate
- Respond to draft policies

Resources

- Final Rule (effective July 5, 2024)
- FDA held an LDT final rule webinar on May 14, 2024 (materials and recording will be available under “In Vitro Diagnostics”)
- *New*: FDA webinar on Enforcement Policies for Certain IVDs – Draft Guidances will be on **June 5, 2024 at 1:00 PM ET**)
  - Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564
  - Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency
  - Comments due July 5, 2024
- Proposed Rule
- APHL comments & guide for commenting

Questions?

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