Background

The Food and Drug Administration (FDA) has clarified their regulatory authority over in vitro diagnostics (IVD) and that they will phase out their enforcement discretion for laboratory developed tests (LDTs). Many public health laboratories (PHLs) perform LDT assay validations that meet Clinical Laboratory Improvement Amendments (CLIA) requirements without any engagement with FDA. The proposed rule explicitly classifies LDTs as devices subject to regulation and, over time, ends the era of enforcement discretion.

Overview

What is a laboratory developed test (LDT)?

An LDT is an in vitro diagnostic device (IVD) that is manufactured and used within a single lab. They are high complexity tests often used for new or rapidly changing conditions or diseases. IVDs are reagents, instruments and test systems intended for the diagnosis of disease or conditions in humans. FDA asserts that LDTs are IVDs and IVDs are devices regardless of where they are manufactured. This includes both those produced by conventional manufacturers and those produced by a laboratory.

Why is the FDA proposing this rule?

LDTs used to be low risk manual assays for diagnosing rare diseases, however many of them now utilize high-complexity instruments and software to test large populations. The FDA is especially concerned about unregulated genetic LDT results that are used to inform critical care decisions such as cancer treatment. The FDA states the risks associated with LDTs are greater today than in 1976 when the system for regulating devices intended for human use was created and that there is a level of variability with LDTs which includes potential for inaccurate or incomplete results. FDA is proposing changes to the LDT oversight to assure their safety and effectiveness.

Other considerations:

- The FDA also suggests current LDTs may exacerbate health inequities because not enough is known about how they perform in underrepresented populations and therefore they may be less accurate with racial and ethnic minorities.
- The FDA believes that regulation will incentivize innovative testing by non-laboratory device manufacturers who may currently be discouraged from developing novel tests due to laboratories developing and marketing similar tests without meeting FDA requirements.
Why can’t LDTs continue to be regulated by CLIA?

The proposed rule states CLIA is not a substitute for FDA oversight. CLIA regulates labs to ensure accurate and reliable results while the FDA regulates manufacturers and devices under the Food, Drug, & Cosmetic (FD&C) Act to ensure the devices are reasonably safe and effective. Although complementary, they differ in scope and purpose with FDA review assessing both analytical and clinical validity.

Will current LDTs be excluded from oversight?

Only if they fall into one of the following categories. All others will be regulated by the proposed rule and as such will need to be approved by the FDA. The proposed rule allows for continued enforcement discretion for the following LDTs:

- Public health surveillance tests: Those used on systematically collected samples in connection with disease prevention and control where the results are not reported to the patient or provider.
- 1976-Type LDTs: Those that use manual techniques performed by lab staff with specialized expertise using components marketed for clinical use in a single CLIA-certified high-complexity laboratory. Examples include manual stains for cytology and certain colorimetric newborn screening tests.
- Forensic tests: Those intended for law enforcement purposes only.
- Human leukocyte antigen (HLA) tests: Those meeting CLIA requirements and used for specific allele typing, antibody screening and monitoring, and crossmatching purposes.

When will this become effective?

The FDA has proposed a four-year, five-stage phaseout of enforcement discretion, noting that a sudden change could negatively impact public health and that agency resources must be considered. The FDA feels that the public health benefits associated with the safety and effectiveness of regulated LDTs will outweigh any issues related to the loss of the LDTs that are withdrawn. They state that it is still “illegal to offer IVDs without complying with applicable requirements” and that they could pursue enforcement action at any time. The phaseout date will align with or follow the start of a new user fee cycle. We do not know what the user fees will be at this time.

Resources

- The proposed rule can be accessed here.
- The FDA offered a webinar on the proposed rule on October 31, 2023. Its recording and slides can be accessed here under “In Vitro Diagnostics/Proposed Rule: Medical Devices; Laboratory Developed Tests”. Questions about the webinar can be emailed to DICE@fda.hhs.gov.
- Previous and upcoming FDA webinars can be accessed here.
- Contact the APHL Public Policy Program with questions or to request a copy of APHL’s response to the proposed rule: Peter Kyriacopoulos, Chief Policy Officer Amanda Cosser, Manager, Regulatory and Public Policy
Instructions for Commenting

- The proposed rule for comment can be found here.
- APHL will submit comments informed by member input. Please share your thoughts or questions with Amanda Cosser, Manager, Regulatory and Public Policy, by November 27, 2023.
- APHL also encourages all members to submit comments by the December 4, 2023 deadline.
  - Submit comments here.
  - Address your letter to:
    Office of the Center Director
    Center for Devices and Radiological Health
    Food and Drug Administration
    10903 New Hampshire Ave, Bldg. 66
    Silver Spring, MD 20993
  - Include the docket number and title of the Federal Register request in your letter.
    - You may wish to use this language in both your letter and the “Comments” box of the online submission: “On behalf of <<Insert Entity Name>> please accept the following comments concerning the Medical Devices, Laboratory Developed Tests (LDT) Proposed Rule, Docket No. FDA-2023-N-2177”.
  - Upload a PDF of your signed letter.

General Talking Points and Recommendations

- Provide comments to help the FDA build the administrative record for continued enforcement discretion of PHL LDTs. Share documents, examples, and supportive information for the agency to rely upon if they move forward with PHL LDT enforcement discretion. APHL would also like to learn about your LDTs so we can resonate your thoughts.
- PHLs strongly believe in accurate, quality, and timely testing and that the FDA has a role in LDT oversight to assure the tests produce reliable results for patients and providers; however, the proposed rule and any associated guidance must not result in unintended consequences that limit or eliminate access to testing or place undue burden on PHLs.
- Developing disease treatment and prevention guidelines, conducting surveillance, and responding to health emergencies are all inherently governmental functions and LDTs are utilized by PHLs to accomplish those goals effectively and efficiently.
- PHLs use LDTs in many programs (infectious diseases, foodborne diseases, biological and chemical threat agents, biomonitoring, and newborn screening) and for many reasons. They are used:
  - When there is no FDA-approved test
  - When the FDA-cleared tests do not meet all population, specimen type, or testing volume needs (examples include expanding to other ages/sources/matrices or automating a manual step in the assay to make it high-throughput)
  - When specimen collection is distant and the acceptable temperature range or turnaround time from collection to testing needs to be expanded
  - Where antimicrobial susceptibility and efficacy must be determined for drugs that may be FDA-cleared for a different indication
- PHLs use LDTs to maintain capability for low incidence, high priority threats such as biological or chemical agents. Many LDTs for these rare agents and diseases have a high test cost and low demand. These tests are currently performed as LDTs at some non-PHLs; however, there is a low likelihood commercial manufacturers will seek FDA approval because the tests do not have a sufficient economic benefit. PHLs need continued enforcement discretion for tests of public health significance so access to
this testing is not limited or eliminated. PHLs do not profit from these tests and perform them for the sole benefit of protecting public health.

- Continued enforcement discretion of unapproved tests during public health emergencies is critical and enforcement discretion should be given for other public health scenarios (this is not an all-inclusive list):
  - Laboratory Response Network – Biological (LRN-B)
  - Laboratory Response Network – Chemical (LRN-C; all LRN-C tests are LDTs as each must be validated at the testing site because laboratory conditions and instruments influence the test)
  - Newborn screening (especially newly added conditions)
  - Emerging pathogens
  - Tests of public health significance such as prion disease (performed almost exclusively at Case Western University), herpes confirmatory testing (performed by Quest and the University of Washington), and HIV-2 testing (performed by the Wadsworth Center and the University of Washington)

- The majority of PHLs have never submitted premarket approval (PMA) or 510(k) documentation and they barely have the staff to perform their daily testing obligations. They are not equipped to redirect staff for filing submissions and do not have the financial resources to pay user fees. PHLs must not have a significant burden placed on staff or their limited operating budget. Each PHL performs dozens to hundreds of LDTs and an alternative reporting approach must be developed for these specialized labs.

- Request clarification on the scope of enforcement discretion for public health surveillance testing which is limited to situations when results are not returned to patients or providers in the proposed rule (see page 53).

- Request enforcement discretion or simplified submission requirements for certain types of modifications to assays with FDA clearance or approval (e.g., stability studies, specimen type or matrix changes, changes in population).

- Request guidance where needed and be specific about what would be helpful. Do you need templates, checklists, flowcharts, or standard operating protocols for determining if a FDA submission is needed, which pathway should be used, and/or for the application package? As written, the proposed rule is not clear on the amount or type of data that would be required for submission of an LDT.
  - Members may wish to ask for templates or protocols similar to those developed by the New York Clinical Laboratory Evaluation Program (CLEP).

- Finally, include a table of the LDTs your lab uses within the letter or as an appendix. Describe their purpose, whether there is a FDA alternative, and the rationale for using the LDT if an FDA-approved test exists. Members may want to include the start date of the LDT use and the number of tests completed annually. You may find the following table helpful. APHL is appreciative of the communicable disease examples from the Wisconsin State Laboratory of Hygiene.

<table>
<thead>
<tr>
<th>LDT Name</th>
<th>Description/Justification of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexually transmitted infections (STI)</td>
<td>Equity focus: Many STI LDTs are validated to broaden acceptable sample collection sites to support STI testing in marginalized communities. For example, testing for GC/CT in persons &lt; 14yo which is needed to reduce the burden for supporting child sexual assault victims.</td>
</tr>
<tr>
<td>Legionella PCR</td>
<td>Detection and differentiation (Legionella species, <em>Legionella pneumophila</em>, and <em>Legionella pneumophila</em> serogroup 1) for clinical diagnostic and public health outbreak response.</td>
</tr>
<tr>
<td>N. meningitidis PCR</td>
<td>Detection of <em>Neisseria meningitidis</em> by PCR to confirm FDA-cleared test results and ensure serogrouping PCR is used on the correct species.</td>
</tr>
<tr>
<td>Test Description</td>
<td>Rationale</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>H. influenzae serotyping PCR</td>
<td>Molecular serotyping to identify which serotypes are circulating, to inform future vaccine formulation and support patient care when vaccine failure is suspected.</td>
</tr>
<tr>
<td>N. meningitidis serogrouping PCR</td>
<td>Molecular serogrouping to determine which strain of <em>N. meningitidis</em> is causing disease, and guide which <em>N. meningitidis</em> vaccine to be used to control outbreaks. Also used to support patient care when vaccine failure is suspected.</td>
</tr>
<tr>
<td>S. pneumoniae antimicrobial susceptibility testing (AST)</td>
<td>Susceptibility testing of an expanded panel of antibiotics not available in FDA-cleared assays, for national antibiotic resistance surveillance.</td>
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<tr>
<td>Lead</td>
<td>Definitive quantitative testing to measure the concentration of the toxic metal lead in pediatric blood specimens. Lead testing identifies children in need of specialized medical treatment (chelation therapy, iron supplementation) and public health interventions (exposure reduction, environmental testing). There is an FDA-approved point of care (POC) test for capillary blood (a screening test) that is less sensitive and specific than the LDTs. The POC test is not appropriate for medical or public health intervention.</td>
</tr>
<tr>
<td>Toxic metal exposures</td>
<td>Definitive quantitative tests to measure toxic metals in clinical specimens including arsenic, mercury, and cadmium. Also, identification of metal species to aid in identification of potential sources of exposure.</td>
</tr>
<tr>
<td>Pesticides, polychlorinated biphenyls (PCBs), organic chemicals</td>
<td>Definitive quantitative measure of toxic organic compounds for public health surveillance, medical management, and/or exposure assessment.</td>
</tr>
<tr>
<td>LRN-C methods: Cyanide, volatile organic compounds, metabolites of warfare agents, metals</td>
<td>Definitive testing for emergency and public health response.</td>
</tr>
<tr>
<td>Newborn screening (NBS) methods</td>
<td>Several PHL NBS methods are LDTs (SCID/SMA and G6PD plus many second-tier assays such as X-ALD and HCMM). Only SCID/SMA has an FDA-approved test; however, it is very expensive (when quoted, the assay cost $6.50 per specimen vs. the LDT cost of less than $1.00). Additionally, predicates do not exist for many NBS LDTs, which would require much time and resources for a submission to FDA. Finally, some FDA-approved tests for NBS assays omit certain populations and are less accurate/less precise than LDTs. Infant lives could be negatively impacted due to these delays, lack of funding, and inequitably focused tests.</td>
</tr>
</tbody>
</table>

*Insert next generation sequencing example*

The FDA has asked specifically for comments on the following. You may choose what you wish to respond to, but please include the rationale behind your feedback.

- Proposed amendment: This rulemaking would amend the definition of “in vitro diagnostic products” in FDA regulations (part 809, subpart A, specifically 21 CFR 809.3) to make clear that IVDs are devices under the FD&C Act “including when the manufacturer of these products is a laboratory”.

November 2023
• Preamble: The preamble describes the proposed approach for the four-year, five-stage phaseout of enforcement discretion. See pages 58-67 of the proposed rule for details on the stages which have low-risk LDTs being phased out last.
  o Members may wish to suggest stratifying the phaseout period by annual test volume. A logical approach may be to regulate high volume LDTs first due to impact on a larger patient population.

• Preliminary Regulatory Impact Analysis
• Whether specific enforcement discretion policies would be appropriate for IVDs offered as LDTs for other public health scenarios (i.e., beyond immediate response to emerging outbreaks).
  o APHL encourages members to consider the information under “General Talking Points and Recommendations” when responding to this question.

• IVDs offered as LDTs by academic medical centers (AMCs):
  o What are the characteristics of AMC labs? Do these characteristics in fact distinguish them from other laboratories?
  o Should FDA continue enforcement discretion for any requirements for tests made by AMC labs? If so, are there any additional considerations that should be taken into account?
  o What would be the public health rationale and evidence to support a different approach for AMCs?

• IVDs offered as LDTs by small laboratories:
  o Is there a public health rationale to have a longer phaseout period for IVDs offered as LDTs by laboratories with annual receipts below a certain threshold (e.g., $150,000)?
  o APHL encourages members to think about whether they fall into this category and to respond accordingly.

• What, if any, unintended consequences may result from the proposed phaseout policy to certain patient populations (for example, Medicare beneficiaries, rural populations, etc.)?
  o APHL encourages members to speak to the unique role PHLs play, such as how they are often the only laboratory providing testing for rare diseases or conditions in rural states, highlighting the LDTs they utilize and emphasizing that access to in-state testing is critical to facilitating a rapid response by the health department and controlling the spread of disease. Please also describe health equity considerations such as how the populations served by PHLs are often uninsured or underinsured.

• Currently marketed IVDs offered as LDTs (i.e., grandfathering current LDTs):
  o Is there a public health rationale for continuing enforcement discretion with respect to premarket review and some or all quality system (QS) requirements, for LDTs that are being offered as of the date of issuance of this proposed rule and are not changed with respect to indications for use or performance after that date?
  o APHL encourages members to consider the information under “General Talking Points and Recommendations” when responding to this question and suggests members mention the staff and financial burden on PHLs as well as the potential unintended consequences of decreasing or limiting access to tests of public health concern. Due to high cost but low demand, many commercial manufacturers may choose to not pursue FDA approval, leaving a void that must be filled. PHLs are often tasked to fill gaps that would negatively affect public health if left unmanaged.

• Leveraging outside programs:
  o Should FDA continue enforcement discretion for any requirements where outside programs can be leveraged?
  o What should the scope of such policy be?
  o What characteristics of and activities within such programs justify such an approach?