FDA 2017 Discussion Paper on Laboratory Developed Tests

Proposes future regulatory oversight on LDTs, including a risk-based, phased-in approach, and amends key provisions of the 2014 draft guidance.

Updated last May 23, 2017 for the 01/13/2017 Discussion Paper.

WHAT IT DOES

The Discussion Paper on Laboratory Developed Tests, released by the Food and Drug Administration (FDA), describes a possible approach to expanding FDA oversight of laboratory developed tests (LDTs). An LDT is a type of in vitro diagnostic (IVD). Specifically, it is a clinical test that is designed, manufactured, and used in a single CLIA-certified laboratory, as opposed to a commercially distributed IVD, which is manufactured and sold for use by many laboratories. The FDA has the authority to regulate all IVDs as devices, but has generally limited its oversight on LDTs, exercising enforcement discretion. However, as LDTs have grown in complexity, number, and reach, the FDA is considering expanding its LDT oversight.

The LDT discussion paper provides an overview of extensive comments received from clinical stakeholders, patients, government agencies, and Congress in response to an LDT draft guidance policy issued by the FDA in 2014. Like the draft guidance, the discussion paper proposes a risk-based approach that the FDA might take on LDT oversight. However, in response to stakeholder feedback, the discussion paper significantly scaled back the scope of the draft guidance's proposed oversight.

Key proposals in the FDA’s 2017 discussion paper include:

- **Focused Oversight:** The FDA would focus oversight on new and significantly modified LDTs of high or moderate risk. Risk would be assessed based on the potential consequences for patients if the LDT were to fail. Previously marketed LDTs would be largely exempt from oversight, although the FDA would retain enforcement discretion for all LDTs.

- **Risk-Based, Phased-in Oversight:** the FDA proposes a four year phased-in approach for premarket review of new and significantly modified LDTs, as opposed to the nine years the 2014 draft guidance. The FDA suggests the following phased-in timeline:
  - Year 1: Serious adverse event and malfunction reporting for all LDTs except: traditional LDTs, LDTs intended solely for public health surveillance, certain stem cell/tissue/organ transplantation LDTs, and LDTs intended solely for forensic use.
  - Year 2: Premarket review for new/modified LDTs with the same intended use as an in vitro diagnostic (IVD) approved under a premarket approval (i.e., tests that have already been identified as high-risk by the FDA).
  - Year 3: Premarket review for new/modified LDTs with the same intended use as a Class II device type subject to 510(k) clearance (i.e., tests that have already been identified as moderate risk by the FDA).
  - Year 4: Premarket review for new/modified LDTs that do not fall into the above categories.

- **Evidence Standards:** the FDA asserts that its clinical and analytical validation and evidence requirements would complement the Centers for Medicare and Medicaid Services (CMS)’s requirements for clinical oversight. “CMS’s oversight through the Clinical Laboratory Improvement Amendments (CLIA) program is designed to confirm that a lab assesses analytical validity, but does not confirm whether it had results from an analytical validity assessment that were sufficient to support the claimed intended use of the test.” However, “laboratories that already conduct proper validation should not experience new costs for validating their test to support marketing authorization.” This document shows how CLIA enforces regulatory oversight over all LDTs.

- **Third-party Review:** the FDA proposes that eligible LDTs could participate in its third-party premarket review program.

- **Clinical Collaboratives:** the FDA proposes to expand its collaborative work with various stakeholders to develop standards for analytical and clinical validity of LDTs.

- **Transparency:** the FDA plans to make analytical and clinical validity reviews of all LDTs publicly available so that the public can understand the test performance and results.

- **Modifications:** the FDA suggests that laboratories include change protocols (plans for anticipated postmarket changes to LDTs) in
their premarket submissions. Once approved, such change protocol would allow the relevant test modifications to be implemented without the need for a new premarket submission.

- CMS/CLIA Quality System (QS) Requirements: the FDA plans to supplement CLIA QS requirements for LDTs with three requirements:
  - Design controls (21 CFR 820.30)
  - Acceptance activities (i.e., mechanisms to ensure product meets specifications throughout testing) (21 CFR 820.80)
  - Procedures for corrective and preventive actions (CAPAs) (21 CFR 820.100).
- Postmarket Surveillance: the FDA proposes postmarket surveillance for LDTs to monitor postmarket modifications and serious adverse events.

The paper does not address conventional IVD kits, which are submitted to more stringent oversight.

The LDT discussion paper is not enforceable, does not represent the formal position of the FDA, and is not a substitute for a final FDA guidance. It synthesizes the regulatory dialogue that the FDA and stakeholders have had since 2010 and outlines future regulatory possibilities for LDTs.

Extensive stakeholder feedback on the 2014 draft guidance highlighted the importance of balancing healthcare access to LDTs with a reasonable assurance that such tests are analytically and clinically valid. The paper is meant to “advance the public discussion” by providing “a possible approach to spur further dialogue.”

**RELEVANT SCIENCE**

LDTs, to include a growing number of genetic tests, serve an important role in health care. In recent years, the cost of genetic testing has dropped and the number of genetic tests available to providers and patients has risen, making them an attractive option for healthcare. The term "genetic testing" refers to a number of techniques used to detect an individual’s genetic variants, including tests that analyze human DNA, RNA, and proteins. Detection of variants associated with a specific disease or condition can be used for screening, diagnosis, prognosis, or treatment plan development. Rapid advancements in the field of genomics have enabled scientists to develop tests to assess an individual’s risk of developing a wide range of diseases.

The successful incorporation of genetic tests into clinical practice – a goal of precision medicine – hinges on the ability to offer the test to the public expeditiously. Most genetic tests available are LDTs, and future genome-based diagnostic tests, including genome sequencing tests, are likely to be LDTs. Developing an FDA-reviewed IVD for the entire genome would be difficult given the millions of bases - and therefore analytes - to review. A clear path for the review of clinical validity of genome-based technologies would likely foster advances in precision medicine.

**RELEVANT EXPERTS**

Sara Katsanis, MS is a Duke University instructor in the Duke Initiative for Science & Society. Her research focuses on policies for DNA testing in medicine, law enforcement, and human rights contexts.

**ENDORSEMENTS & OPPOSITION**

Endorsements:

- **Office of Public Health Strategy and Analysis**, “We examined events involving 20 LDTs that illustrate, in the absence of compliance with FDA requirements, that these products may have caused or have caused actual harm to patients.”
- **American Medical Association**: “Many of the proposed changes are consistent with recommendations suggested by physician organizations, but ongoing dialogue will be needed to address remaining issues of concern that could impede innovation,”
particularly for rapidly evolving testing services and procedures used to detect infectious disease outbreaks.”

- American Clinical Laboratory Association: “The clinical laboratory community is pleased the FDA acknowledges that stakeholder input and the ongoing bipartisan work by Congress is the appropriate process to advance comprehensive reform of the LDT regulatory framework.”

- American Cancer Society and 32 other healthcare organizations sent a letter to Senate leadership urging them to update rules for oversight for all diagnostic tests, including LDTs. The letter said that they feel the FDA should “play a critical role in a modernized framework that supports patient safety and access to valid tests.” “The FDA is the most appropriate agency to evaluate the analytical and clinical validity of diagnostic tests, along with their safety, to help ensure that cancer patients and their doctors are able to make appropriate treatment decisions based on accurate information. In an era of precision cancer medicine, diagnostic tests are the foundation of personalized care and oversight is imperative to ensure the foundation can be trusted.”

- Association for Molecular Pathology: “We are pleased that the FDA has decided not to finalize the guidance and we look forward to our continued discussions and professional collaborations to ultimately develop a streamlined approach that ensures high-quality patient care, enhances transparency, and preserves innovation.”

Opposition:

- AdvaMedDx, the medical device industry trade group which is in favor of increased FDA oversight of LDTs: “disappointed that FDA final guidance on LDT oversight is not forthcoming at this time, but we are encouraged by congressional interest in addressing longstanding questions about LDT regulation in the context of broader diagnostics reform legislation.”

STATUS

The Discussion Paper on Laboratory Developed Tests was published on January 13, 2017. The purpose of the discussion paper is to “advance the public discussion by providing a possible approach to spur further dialogue.” Beyond this, the FDA has not formally solicited feedback or indicated plans for future LDT-related guidances.

RELATED POLICIES

Federal agencies’ roles in the regulation of genetic tests include:

- CMS requires that laboratories meet certain standards related to personnel qualifications, quality control procedures, and proficiency testing programs in order to receive CLIA certification. However, CLIA does not require evaluation of the [clinical validity or utility](https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/CLIA2002-Regulations.pdf) of any particular test.
- The FDA regulates IVDs as devices under the [Medical Devices Amendments](https://www.fda.gov/MedicalDevices/) (1976) and [Federal Food, Drug, and Cosmetic Act](https://www.govinfo.gov/content-details.action?id=158034) (1938). “The term “device” ... means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article ...” (section 201(h) of the FDCA ([21 U.S.C. 321(h)](https://www.law.cornell.edu/uscode/text/21/321)). The FDA assesses a device's accuracy, clinical sensitivity, and specificity. Currently, few genetic tests are commercial distributed IVDs; most are LDTs developed and performed by laboratories.

Other related documents include: Guidance on “[Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only](https://www.fda.gov)” for Industry and Food and Drug Administration Staff.

POLICY HISTORY

On June 16, 2010, the FDA [announced](https://www.fda.gov) its intention to expand its regulatory oversight of LDTs, after years of maintaining an
enforcement discretion policy while declining to closely regulate LDTs. The FDA argued that LDTs had evolved and proliferated significantly from being relatively simple lab tests which were available on a limited basis, confined to local labs, and often used for rare conditions.

Following the FDA’s announcement in 2010 that it was reconsidering policy enforcement discretion over LDTs, the agency held a workshop to obtain input from stakeholders. Using this feedback, the FDA developed and published draft guidance in October 2014. Moving forward, the FDA solicited feedback on the draft LDT framework and notification guidances and held a public workshop in 2015 to incorporate the extensive stakeholder feedback.

The FDA decided not to issue a final guidance and instead formulated a synthesis of the stakeholder feedback and its response to that feedback in the discussion paper, which was released January 13, 2017.