# FDA Unveils Anticipated Draft Guidance for the Regulation of Laboratory-Developed Tests

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## Overview

On July 31, 2014, the Food and Drug Administration (FDA) provided Congress notice of its intent to issue draft guidance providing a risk-based framework for the regulation of laboratory developed tests (LDTs) under the agency's medical device oversight authority. The agency released two documents that provide detail on the anticipated regulatory framework for LDTs. The first document is titled "Framework for Regulatory Oversight of Laboratory Developed Tests," and would regulate LDTs "in a manner that is consistent with FDA's current regulation of *in vitro* diagnostic devices." This represents a significant departure from the agency's long standing position of "enforcement discretion" in regulating clinical diagnostic tests performed by a laboratory, and not sold as a kit. FDA notes that it is concerned about gaps in regulation of LDTs under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), and in particular that CLIA does not assure the safety and effectiveness of LDTs, require adverse event reporting, nor require removal from the market of tests deemed unsafe.

A second document entitled "FDA Notification and Medical Device Reporting for Laboratory Developed Tests," would establish a new "notification procedure" for certain LDTs in lieu of annual registration and listing with FDA. Under the envisioned notification procedure, LDT laboratories would initially submit on-line through the FDA website basic information about the LDT to FDA, and the agency would use the data to implement the risk-based enforcement. Medical device reporting refers to the reporting of substantial injuries or mortality caused by device malfunction.

FDA's statutory authority to regulate LDTs has been questioned by some stakeholders, most notably in a Citizen's Petition to FDA from the American Clinical Laboratory Association (ACLA) in June, 2013. ACLA argued that LDTs do not meet the definition of a device under the Food, Drug, and Cosmetic Act (FD&C Act). Concurrently with the notifications, FDA released a response to ACLA's citizen petition, denying ACLA's request to refrain from regulating LDTs as devices[1].

In what is expected to be the first step in a lengthy process, FDA was required to notify Congress 60 days in advance of its promulgating a guidance concerning the regulation of LDTs under the Food and Drug Administration Safety and Innovation Act of 2012 (Pub. L. 112-144, Sec. 1143). Therefore, the upcoming draft guidance will not be formally released until October 1, 2014 at the earliest, and at that time the agency will open a docket for public comment. Importantly, FDA anticipates that enforcement of the new requirements over LDTs would be phased in following the issuance of a final guidance over several years:

- Laboratories providing LDTs (except a few exempted categories) would comply with notification or registration/listing, and adverse event reporting, within 6 months of the issuance of the LDT final guidance.
- FDA would phase in its enforcement of premarket review and Quality System Regulation (QSR) —prioritizing by risk— over a period of nine years after the publication of the LDT final guidance.

The LDT notification document prioritizes the application of other regulatory requirements by risk. Three specific high risk categories of LDTs would be subject to premarket review within 12 months of the issuance of the final LDT guidance (for existing LDTs) or immediately upon finalization of the guidance (for LDTs introduced after the final guidance is issued). These high risk LDT categories would include tests with the same intended use as a cleared or approved companion diagnostic or an approved Class III in vitro diagnostic test. Advisory panels would assist the FDA in classifying other LDTs into a risk based set of categories over a two-year period. FDA refers to the

resulting categorization as a "priority list."

The new LDT notification documents address but do not answer several critical issues. While "high-risk" tests would be first to be subject to premarket review, there is little to illuminate precisely how FDA intends to assess risk, which intended use and diagnostic claims will be permissible or feasible, or what types and amounts of evidence will be required in premarket review. The notification documents do not reconcile medical device requirements with CLIA compliance, except in a general fashion. Laboratory stakeholders have raised concerns that the FDA's manufacturing operations and quality control are ill-fitted to laboratory test procedures. The notifications also do not distinguish between clinical laboratory and physician pathology laboratory tests, both of which are regulated together under CLIA, but allow exemptions for tests that require "interpretation," which may often be the case for complex genetic tests.

Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health (CDRH), noted on a call with industry stakeholders that FDA would not require the payment of user fees for LDT laboratories. However, it is unclear how the FDA would resource its premarket review of potentially thousands of LDTs newly subject to premarket review, or how LDTs would fare in future negotiations over medical device user fees. Nor does the notification address whether the medical device tax or disclosure under the Physician Payment Sunshine Act will apply to LDTs registered with, versus cleared or approved, by FDA.

Additionally, FDA released the final guidance for companion diagnostics. The draft guidance was released in July, 2011. Since that time FDA has approved 18 companion diagnostics for use with targeted anti-cancer therapeutic agents.

Below are a timeline and a summary of the key terms and provisions.

### Proposed Timeline of Implementation

Click here to see table.

**Definition of an LDT**

- Definition. The notification document defines an LDT as an in vitro diagnostic device (IVD) that is intended for clinical use and designed, manufactured and used within a single laboratory (i.e. a facility with a single CLIA certificate).
    - Exclusions. The definition does not include tests that are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them. Nor does the definition include direct-to-consumer (DTC) tests.
- Tests currently offered as LDTs. FDA proposes to apply the same risk-based framework to tests that are currently offered as LDTs, even if they do not meet FDA's definition of an LDT.

**Risk-Based Framework**

FDA will rely upon the existing medical device classification system to evaluate the risk of a category of LDTs. The notification sets out a process to identify LDTs as Class I (low risk), Class II (moderate risk), and Class III (high risk).

- Highest risk categories. FDA identified three "highest risk" categories of LDTs, which would be at the top of FDA's enforcement priorities:
    - LDTs with the same intended use as a cleared or approved companion diagnostic;
    - LDTs with the same intended use as an approved Class III medical device; and
    - Certain LDTs used to determine safety/efficacy of blood or blood products.
- Higher concern LDTs. FDA also identified the following categories of high risk LDTs as being of "higher concern" to the agency, immediately below the highest risk categories:
    - LDTs that act like companion diagnostics;
    - Screening LDTs for serious diseases or conditions intended for use in asymptomatic patients with no other available confirmatory diagnostic product or procedure, such as screening device for malignant cancers; and
    - Diagnostic LDTs for certain infectious diseases with high risk intended uses.
- Risk classification considerations. In determining the risk an LDT poses to the patient or the user, FDA would consider several factors including—

- whether the device is intended for use in high risk disease/conditions or patient populations,
- whether the device is used for screening or diagnosis,
- the nature of the clinical decision that will be made based on the test result,
- whether a physician/pathologist would have other information about the patient to assist in making a clinical decision (in addition to the LDT result),
- alternative diagnostic and treatment options available to the patient,
- the potential consequences/impact of erroneous results,
- number and type of adverse events associated with the device, and
- potentially other factors.

- Advisory Panels. FDA would utilize advisory panels to help classify LDTs not previously classified by FDA, as appropriate.
- Guidance on classification. FDA would issue a draft guidance to describe which LDTs it considers to be Class I, II, or III within 18 months of the finalization of this guidance; and a final guidance within 24 months of the finalization of the LDT guidance.
- Low-risk categories. FDA identified four categories of LDTs, which pose a low risk to patients, and would therefore be subject only to notification or registration/listing, and adverse event reporting requirements:
  - LDTs used for rare diseases (4,000 patients per year or less)
  - Traditional LDTs (type of LDTs that were available in 1976, and LDTs used within a hospital network for its own patients)
  - LDTs for unmet needs (as long as there is no cleared/approved alternative)
  - Class I (low-risk) LDTs

**Application of Regulatory Requirements to LDTs**

The two notification documents establish a new regulatory framework for LDTs with four core requirements: notification (or registration and listing), adverse event reporting, premarket review, and QSR requirements. The implementation of these requirements and level of oversight is based on risk as detailed below.

1. Notification in lieu of registration/listing.

- A new notification process would be created under a separate guidance document "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)".
- Applicable to all non-exempt LDTs within 6 months of the issuance of final LDT guidance. Laboratories could choose to undergo a one-time notification process in lieu of compliance with medical device registration and listing requirements.
  - Significant changes to an LDT would require an additional notification.
- Notification information should be submitted online through the FDA website. The following data would be required for a notification:

  laboratory name; test name; monthly test volume; intended use; clinical use of test; what is measured or detected; disease / condition for which the diagnostic device is indicated; patient population and whether includes pediatric; sample type; test method; and whether the test a modification of an FDA cleared/approved test, and which modifications were made.

2. Medical device reporting.

- Applicable to all non-exempt LDTs within 6 months of the issuance of final guidance.
- LDT laboratories would be required to fulfill the MDR requirements for manufacturers (in addition to the requirements for user facilities) for all reportable events involving an LDT manufactured by the laboratory. Unlike user facilities, manufacturers are required to—
  - report serious injuries to FDA rather than to the manufacturer;
  - fill out additional sections of MedWatch 3500A form;

- report certain device malfunctions; and
- submit five day remedial action event reports to FDA.

3. Premarket review.

- FDA intends to phase in the enforcement of applicable premarket requirements over time based upon the risk associated with that device. FDA intends to focus its efforts on the "highest risk" devices first and gradually phase in enforcement for other Class III and Class II devices over time.
- Phased in over 9 years:
  - *"Highest risk" Class III*: begins 12 months after issuance of final guidance.
  - *Class III high risk*: begins 36 months after issuance of final guidance.
  - *Class II moderate risk*: begins 5 years after issuance of final guidance.
- FDA believes it would not be necessary for sponsors to conduct extensive new studies to demonstrate clinical validity of analytes/markers where an LDT's analytes/markers that are measured/assessed have had their clinical validity already established in the literature, so long as the changes to technology or methodology that differ from that used in the literature to assess the analyte/marker do not affect the clinical validity of the LDT.
- FDA could delegate the review of 510(k) applications for most moderate risk (Class II) LDTs to accredited third-party reviewers.
- CDRH Director, Dr. Jeffrey Shuren, stated on a call with industry stakeholders that LDTs would not be subject to user fees.

4. Quality System Regulation requirements.

- FDA intends to continue to exercise enforcement discretion with respect to the QSR requirements until a laboratory of a given LDT submits a premarket approval application (PMA) or FDA issues a 510(k) clearance order for the LDT.
- This initial period of continued exercise of enforcement discretion for QSR requirements is intended to allow time for laboratories to learn about their regulatory obligations. The agency will phase in the QSR requirements as follows:
  - *"Highest risk" Class III*: Enforced once a PMA is submitted or FDA issues a clearance order.
  - *Class III*: QSR requirements applicable when a laboratory submits a PMA.
  - *Class II*: QSR requirements are applicable to a laboratory following FDA 510(k) clearance order for the LDT.
- FDA would consider expanding its third-party inspection program for surveillance inspections and exploring opportunities to coordinate and leverage existing programs.
- On a call with industry stakeholders, Dr. Shuren noted that FDA will consider relying on CLIA inspectors to inspect compliance with QSR requirements as well.

**LDTs Exempt from Regulatory Requirements**

- Categories of exempt LDTs. FDA will continue to exercise full enforcement discretion for two categories of LDTs:
  - LDTs used solely for forensic (law enforcement) purposes; and
  - Certain LDTs for transplantation when used in CLIA-certified, high complexity histocompatibility laboratories.
- Enforcement discretion. For these categories of LDTs, there would not be any regulatory requirements enforced under the FD&C Act.

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1. [See Docket No. FDA-2013-P-0667]

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