

## Food and Drug Law Alert

August 13, 2014

### FDA Takes First Steps Towards Regulating Laboratory Developed Tests

On July 31, the Food and Drug Administration (FDA or “the Agency”) notified Congress that it intends to issue draft guidance proposing a Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) (“Draft [Framework Guidance](#)”). LDTs are a type of *in vitro* diagnostic (IVD) developed and used within a single laboratory. After several years of anticipation, FDA has taken the first step toward a new framework under which many LDTs will ultimately be regulated in the same way as other diagnostic tests. As described in greater detail below, the anticipated details of FDA’s proposed LDT policy include the following:

- *What is (and is not) an LDT:* The Draft Framework Guidance clarifies what the Agency considers to be an LDT, and what characteristics would disqualify a diagnostic test from LDT status. FDA also emphasizes that direct-to-consumer (DTC) tests will not qualify for the proposed LDT framework even if they otherwise qualify as an LDT.
- *Proposed regulatory framework:* FDA proposes a risk-based, phased-in approach under which LDTs will be divided into four categories of oversight. Lower risk LDTs will continue to receive varying levels of enforcement discretion. Moderate- and high-risk LDTs will be ultimately subject to regulatory requirements in accordance with the existing Class II and Class III device requirements, respectively.
- *Notification Requirements:* For many of the LDTs that will remain subject to enforcement discretion, FDA plans to require notification in lieu of registration and listing; this proposal is described in a separate [Draft Notification Guidance](#) (see page 45).
- *Timeline for Implementation:* The Draft Framework Guidance provides a timeline for implementing the new regulatory scheme, which will take place on a rolling basis over the course of 10 years. High-risk LDTs will be required to begin making premarket submissions 12 months after the guidance is finalized, and moderate-risk LDTs will be required to begin making premarket submissions beginning the fifth year after the guidance is finalized.

Given the rapid growth of the diagnostic testing industry—and genetic testing, in particular—FDA’s posture regarding LDTs has significant implications for labs and other diagnostics companies, as well as the hospitals and patients that rely on these tests. Although this is a significant first step, it is just the beginning of what will be a lengthy and hotly debated process. Stakeholders and members of Congress can be expected to weigh in extensively, and legal challenges are anticipated. FDA is likely to release the Draft Framework Guidance formally for public comment at the end of September.

## Background

LDTs, sometimes called “homebrew” tests, are *in vitro* diagnostics invented and used by a laboratory. These labs may be independent or affiliated with a hospital system, and operate under a Clinical Laboratory Improvement Amendments of 1988 (CLIA) certificate. Up to now, the Agency has exercised enforcement discretion over these tests, meaning that FDA does not actively enforce its regulatory requirements but reserves the right to do so in the future or in particular instances. In contrast to LDTs, many *in vitro* diagnostics are manufactured and sold to a health care facility for the facility’s use; these tests are generally subject to FDA regulation as medical devices.

FDA maintains that *in vitro* diagnostics are medical devices whether they are LDTs or not. Some LDT sponsors have indeed sought and received clearance from FDA as a medical device. In recent years, the Agency has expressed growing concern about the proliferation of LDTs; the Agency has questioned whether LDTs are safe and effective for their intended uses given that they are not being held to the same premarket clearance, adverse event reporting and quality assurance requirements applicable to other diagnostic tests. Specifically, FDA has asserted that a lab’s CLIA certification does not guarantee the accuracy and reliability of each of the lab’s LDTs, as must be demonstrated pursuant to the premarket clearance or approval for diagnostic devices under the federal Food, Drug, and Cosmetic Act (FDCA). In contrast, some stakeholders disagree that FDA has authority over LDTs, and believe that FDA oversight is unnecessary and would be unduly burdensome.

In 2010, FDA announced plans to lift its policy of enforcement discretion for LDTs and adopt a risk-based approach that would be described in draft guidance. In anticipation of a new regulatory approach to LDTs, FDA invited the clinical lab community to participate in the user fee negotiations with the medical device industry that commenced in the beginning of 2011 (which culminated in the Medical Device User Fee Amendments 2012, or MDUFA III). LDT legislation was subsequently introduced in Congress, and the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) required the Agency to provide Congress 60 days’ notice prior to issuing guidance relating to LDTs. It is in fulfillment of this FDASIA notification mandate that FDA has now announced the “anticipated details” of its long-awaited draft guidance on LDTs.

## Highlights

### What is (and is not) an LDT

Up to now, FDA has provided limited guidance on precisely what constitutes an LDT for purposes of falling within the Agency’s grant of enforcement discretion. The term LDT has sometimes been used colloquially to refer to any lab-sponsored *in vitro* diagnostic that hasn’t gone through the FDA approval process. The Agency’s view was obviously narrower, but could be only partially divined via warning letters and informal statements. The Draft Framework Guidance provides greater clarity, emphasizing that an LDT must be designed, manufactured and used within a single laboratory under a single CLIA certificate. In the interests of “continuity,” however, the Agency intends to include tests marketed by CLIA labs as LDTs under the proposed regulatory framework, even if they do not meet FDA’s definition of LDTs. Notably, however, direct-to-consumer (DTC) tests—another significant area of innovation—will not qualify

for the proposed LDT framework even if they otherwise qualify as an LDT. They will potentially be subject to active regulation as a medical device without a phased-in framework.

### **Proposed regulatory framework for LDTs**

Using a risk-based approach, FDA proposes to classify LDTs into three categories: (i) LDTs subject to full enforcement discretion; (ii) LDTs subject to partial enforcement discretion; and (iii) LDTs subject to full FDA regulation as diagnostic devices.

**Full Enforcement Discretion.** FDA plans to continue to exercise enforcement discretion for all applicable regulatory requirements for LDTs used solely for law enforcement purposes and certain LDTs for transplantation, when used in CLIA-certified, high-complexity histocompatibility laboratories.

**Partial Enforcement Discretion.** The Agency will exercise enforcement discretion for premarket review and quality systems requirements, but enforce other applicable regulatory requirements (including registration and listing, and adverse event reporting) for:

- *Low-risk LDTs:* Those classified as Class I devices under the existing medical device risk-based classification scheme.
- *LDTs for Rare Diseases and “Traditional LDTs”:* To qualify as an LDT for a rare disease, the test must be used to test fewer than 4,000 patients per year in accordance with the Humanitarian Use Device definition. FDA defines “Traditional LDTs” as “types of LDTs [that] reflect the types of LDTs that existed when the enforcement discretion policy was initially implemented.” The Agency identifies several factors for determining whether an LDT is “traditional,” including:
  - whether the LDT is both manufactured and used by a health-care facility laboratory for a patient being diagnosed and/or treated in the same facility or in the same system
  - whether the LDT is comprised of only legally marketed components and instruments
  - whether the LDT is “interpreted by qualified laboratory professionals without the use of automated instrumentation or software for interpretation.”
- “LDTs for Unmet Needs”: FDA will consider a number of factors to determine if an LDT is designed for unmet needs, including:
  - whether there is no FDA-cleared IVD for the specific intended use
  - whether the LDT is both manufactured and used by a health care facility laboratory for a patient being diagnosed and/or treated in the same facility or in the same system.

For those LDTs subject to partial enforcement discretion, sponsors are to register and list (with the option to provide notification) with FDA and begin adverse event reporting within six months of the Guidance

being finalized. For new LDTs offered after that six-month period, a new notification should be provided prior to offering that LDT for clinical use.

**Full Regulation.** FDA plans to enforce full regulatory requirements for high- and moderate-risk LDTs, including registration and listing, adverse event reporting, premarket review and quality system requirements.

- *High-Risk LDTs:* The Draft Framework Guidance identifies the types of LDTs that the Agency considers high risk: LDTs with the same intended use as an FDA-approved Class III device; LDTs with the same intended use as a cleared or approved companion diagnostic; and, certain LDTs for determining the safety or efficacy of blood or blood products.
- *Moderate-Risk LDTs:* Moderate-risk LDTs are those classified as Class II devices (unless otherwise treated as high risk, pursuant to the criteria listed above).

### **Notification Requirements**

FDA also released “anticipated details” of a [Draft Notification Guidance](#) on FDA Notification and Medical Device Reporting for LDTs in conjunction with the notice to Congress. For all LDTs, FDA intends to exercise enforcement discretion over establishment registration and listing so long as laboratories notify FDA of their LDTs within six months of the Draft Notification Guidance being finalized. Going forward, the Agency will continue to allow notification in lieu of registration and listing for those LDTs subject to enforcement discretion. For moderate- and high-risk LDTs that are required to seek FDA clearance or approval, however, FDA intends to enforce registration and listing requirements beginning with the product’s premarket submission . Finally, the Draft Notification Guidance will subject labs with LDTs to many of the same requirements applicable to medical device manufacturers, including Medical Device Reporting (includes adverse event reporting) and reporting of corrections and removals.

### **Timeline for Implementation**

For high- and moderate-risk LDTs, registration and listing (with the option to provide notification) and adverse event reporting are slated to begin six months after the Draft Framework Guidance is finalized. For the high-risk category, LDTs must begin submitting premarket submissions within 12 months after the guidance is finalized, and will be phased in over the course of four years. In the fifth year, moderate-risk LDTs must begin submitting premarket submissions. Laboratory compliance with relevant Quality System regulations begins at the time of PMA submission or 510(k) clearance.

Even for those LDTs subject to full regulation and premarket submissions, FDA committed to the lab industry in the last round of medical device user fee negotiations that the Agency would waive user fees for LDTs during MDUFA III (fiscal years 2013 through 2017). During MDUFA III deliberations, FDA announced in stakeholder meetings that it intended to utilize a newly negotiated discretionary fee-waiver provision (which allows the Secretary of Health and Human Services to waive or reduce application and registration fees in the interest of public health) for LDTs “if FDA changes its policy of enforcement discretion for laboratory developed tests (LDTs) during MDUFA III.” The discretionary fee waiver provision,

which sunsets at the end of MDUFA III, only authorizes fee waivers for up to two percent of total fee amounts in a given year.

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