FDA Releases Long-Awaited LDT Regulatory Framework and Finalizes Companion Diagnostics Guidance

On July 31, 2014, the Food and Drug Administration (FDA) took several significant actions to clarify its policies regarding regulation of certain in vitro diagnostic devices (IVDs). First, FDA released its long-awaited plan for the regulation of laboratory developed tests (LDTs). Second, FDA denied three citizen petitions related to regulation of LDTs. Third, FDA issued final guidance on in vitro companion diagnostic devices. Although the companion diagnostics guidance is likely to be relatively uncontroversial, the LDT framework's release represents the first step in a multi-year process that could spur legislative activity or legal challenges and may have significant effects on the future market for diagnostic tests.

Notification to Congress: Framework for Regulating LDTs

In section 1143 of the Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in 2012, Congress required FDA to provide a 60-day notification before issuing any draft or final guidance on the regulation of LDTs. FDA has complied with that requirement by delivering two proposed guidance documents: *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* (Framework Guidance) and *FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)*. Section 1143, originally proposed by opponents of FDA regulation of LDTs, presumably was intended to allow Congress to react to any FDA proposal to regulate such tests. In the current political environment, however, any meaningful congressional activity is unlikely in the near term. As a result, FDA will likely formally publish these guidance documents this fall.

A. Framework Guidance

In the Framework Guidance, FDA announces its intention to regulate LDTs, marking a change from its long-standing policy of exercising enforcement discretion with respect to these diagnostic tests. The proposed framework would phase in FDA regulation over nine years (and possibly longer, depending on FDA resources), with the level of premarket and postmarket oversight varying according to risk. As described by the Director of FDA's Center for Devices and Radiological Health (CDRH), FDA's intent is to adopt a risk-based oversight framework with phased implementation "beginning with the highest-risk tests (which include companion diagnostics- crucial to personalized medicine by targeting treatments for cancer, heart disease and other conditions) to give laboratories time to comply."[1]

Scope. The proposed framework applies to LDTs. The guidance defines LDT as "an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory." FDA states that it is aware that some laboratories may currently be offering devices as LDTs even though they do not meet FDA's definition (e.g., laboratories that have licensed the rights to a diagnostic test from another entity). Nevertheless, to avoid disrupting access to these tests, FDA states that it intends to apply the proposed guidance's risk-based framework to any IVD offered as an LDT by a CLIA-certified laboratory. By contrast, FDA states that the proposed guidance does not apply to direct-to-consumer (DTC) diagnostic tests, as FDA's policy is generally not to exercise enforcement discretion with respect to such tests even if they satisfy the definition of an LDT.

Need for FDA Oversight of LDTs. The proposed guidance asserts that FDA has long had statutory authority to regulate LDTs, but historically has chosen to exercise enforcement discretion, leaving their regulation to Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). FDA justifies its proposed policy shift on the nature of modern LDTs, which are

[1] Jeffrey Shuren, *Curbing Risk, Not Medical Innovation, in Personalized Medicine*, FDA Voice (July 31, 2014), available here.

often offered beyond local populations and manufactured in high volume, used widely to screen for common diseases, used to direct critical treatment decisions (e.g., prediction of drug response), and involve non-transparent algorithms, automated interpretation, or other highly complex features. As a result, FDA says, such tests are not adequately addressed by CLIA requirements, which do not assess analytical or clinical validity of LDTs prior to their marketing, require adverse event reporting, require removal of unsafe devices from the market, impose manufacturing quality standards, or require informed consent for patients who participate in LDT clinical studies.

Risk-Based Regulatory Framework. Recognizing the wide range of risks associated with LDTs, FDA states that it intends to implement a risk-based regulatory approach.

1. Devices Receiving Continued Enforcement Discretion for All Applicable Regulatory Requirements. FDA intends to continue to exercise enforcement discretion for all applicable regulatory requirements for two categories of LDTs:
   - (1) LDTs used solely for forensic (law enforcement) purposes, and
   - (2) Certain LDTs for transplantation when used in CLIA-certified, high-complexity histocompatibility laboratories.
2. Devices Receiving Enforcement Discretion with Respect to Premarket Review and Quality System Requirements. FDA intends to exercise enforcement discretion for applicable premarket review requirements and Quality System Regulation (QSR) requirements, but enforce other applicable regulatory requirements, including registration and listing and adverse event reporting, for the following:
   - (1) Low-risk LDTs (Class I devices),
   - (2) LDTs for rare diseases and "Traditional LDTs" that reflect the types of LDTs that existed when the enforcement discretion policy was initially implemented, and
   - (3) "LDTs for Unmet Needs," when no FDA-approved or cleared equivalent device is available.
3. Devices No Longer Receiving Enforcement Discretion. For other high and moderate risk LDTs, FDA intends to enforce applicable regulatory requirements, including registration and listing, adverse event reporting, premarket review, and QSR requirements.

Timeline. FDA intends to phase in regulation of LDTs over several years in order to balance the need to ensure safety and effectiveness of LDTs with the need to provide sufficient time for implementation. The guidance describes the following timeline:

1. Registration and Listing/Notification and Adverse Reporting. Six months after final guidance is issued, manufacturers of LDTs should notify FDA if they are developing LDTs and must begin to report significant adverse events to FDA.
2. Premarket Review. FDA will rely upon the existing medical device classification system to evaluate the risk of a category of LDTs, using expert advisory panels to help classify devices not previously classified by FDA, and intends to issue draft guidance to describe what it considers generally to be Class I, II, or III within 18 months of finalization of the framework guidance. FDA intends to phase in enforcement of premarket review requirements for LDTs over time based on relative risk. The phased enforcement, starting with the highest-risk devices, will begin 12 months after the guidance becomes final. FDA also states that clinical literature will often be available to support the clinical validity of an LDT, which should lessen the burden of obtaining premarket approval or clearance of such tests.
   - *High-risk LDTs (Class III medical devices)*: Premarket review requirements begin 12 months after this guidance is finalized for the "highest risk devices" and phase-in over four years for the remaining high-risk devices. The "highest risk devices" are (1) LDTs with the same intended use as a cleared or

approved companion diagnostic, (2) LDTs with the same intended use as an FDA-approved Class III medical device, and (3) certain LDTs for determining the safety or efficacy of blood or blood products. FDA believes that most high-risk LDTs will require a premarket approval (PMA) application.

- *Moderate-risk LDTs (Class II medical devices)*: Premarket review requirements begin after the review of high-risk (Class III) LDTs is completed, meaning five years after the guidance is finalized, and phase-in over four years. FDA expects that such devices will require 510(k) clearance rather than PMA approval and that accredited third parties will carry out most of these 510(k) reviews. Once a category of LDT is "called in" for premarket review, laboratories will have 12 months to submit a premarket application for their LDT if FDA clears a test in that category.

Aside from the "highest risk devices," FDA will prioritize enforcement of premarket review requirements for other LDT categories based on risk using a public process, including expert advisory panels as appropriate. The number and type of LDTs "called in" for premarket review at a given time will be "commensurate with available agency resources." Priority lists will be published describing the order and timeframe in which the agency intends to enforce premarket review requirements for different categories of LDTs. FDA expects to announce the priority list for high-risk, Class III, devices within 24 months from finalization of the guidance, with enforcement to commence 12 months after such announcement. FDA expects to announce the prioritization of moderate-risk, Class II, LDTs within four years of issuing final guidance and expects to complete phased-in enforcement of premarket requirements for such devices within 9 years of finalizing the guidance.

3. Quality System Regulation. Under the proposed framework, laboratories that manufacture LDTs would comply with the QSR when a premarket approval application (PMA) is submitted or FDA issues a 510(k) clearance order for the LDT.

B. Notification and Medical Device Reporting Guidance

In addition to the Framework Guidance, FDA's notification to Congress included a proposed companion guidance providing additional direction on the notification and medical device reporting requirements for LDTs.

Notification. As stated in the Framework Guidance, FDA will require most LDTs to comply with registration and listing requirements within six months of issuance of final guidance. However, as an alternative, FDA intends to continue to exercise enforcement discretion with respect to registration and listing requirements provided that clinical laboratories notify FDA that they are manufacturing LDTs and provide basic information regarding each of these LDTs within this six-month timeframe. Laboratories that provide such notifications will not need to pay annual establishment user fees to FDA. FDA intends to make such notifications public.

Notably, FDA states that establishments that manufacture other devices in addition to LDTs will not have the option of using the notification process and must comply with registration and listing requirements for their LDTs. In addition, once a laboratory has submitted a PMA or 510(k) to the FDA, FDA will require compliance with registration and listing requirements.

Medical Device Reporting. FDA intends to enforce the MDR regulations at 21 C.F.R. Part 803 with respect to laboratories manufacturing LDTs. Laboratories manufacturing LDTs would be required to comply with MDR requirements as both device user facilities and as device manufacturers. Laboratories would be

responsible for reporting adverse events to FDA within the timeframes established in the regulations, as well as developing, maintaining, and implementing written MDR procedures and MDR event files.

Citizen Petition Responses

On the same day FDA issued the above notification to Congress of its intention to regulate LDTs, the agency denied three citizen petitions relating to the regulation of LDTs.[2] The three petitions highlight the highly contentious nature of the issue of FDA oversight of LDTs. There could well be a messy fight ahead, with the potential for protracted litigation.

Two of the petitions denied by FDA—the American Clinical Laboratory Association (ACLA) and Washington Legal Foundation (WLF) petitions—asserted, among other things, that the FDA lacks statutory authority to regulate LDTs. The ACLA petition further argued that FDA regulation of LDTs would be contrary to the public health, stifling innovation and limiting patient access to crucial diagnostic testing. FDA denied the ACLA and WLF petitions on all grounds. With respect to the ACLA's arguments that FDA regulation of LDTs would harm the public health, FDA stated that its oversight is crucial to protecting the public health, as CLIA alone does not adequately assure safety and effectiveness of modern LDTs.

The third petition FDA denied was submitted by Genentech. In contrast to the ACLA and WLF petitions, Genentech argued that FDA does possess authority to regulate LDTs and requested, among other things, that FDA establish regulations governing all LDTs and take enforcement action against laboratories selling LDTs that have not been approved or cleared. FDA agreed with Genentech that it has the authority to regulate LDTs and that there are strong public policy reasons for exercising regulatory oversight over LDTs, but rejected Genentech's specific requests for agency action.

Final Guidance on Companion Diagnostics

FDA finalized its guidance on companion diagnostic devices with very few changes from the draft guidance released in 2011.

Scope. The guidance addresses the development, approval, and labeling of both IVD companion diagnostic devices and the corresponding therapeutic products. The guidance applies to therapeutics for which the use of an IVD is "essential for safe and effective use" and to the corresponding IVDs. "Essential" means that "use of a diagnostic device is required in the labeling of a therapeutic product."

Contemporaneous Development and Approval. The guidance provides that IVD companion diagnostic devices and the corresponding therapeutic products should generally be developed contemporaneously. Sponsors are encouraged to meet with both the relevant therapeutic and device review divisions early in development. FDA review of the IVD companion diagnostic device and therapeutic product will be carried out collaboratively among relevant FDA offices.

The guidance further provides that, if an IVD is essential to the safe and effective use of a novel therapeutic product or indication, FDA generally will not approve the therapeutic product or new indication if an IVD companion diagnostic device is not approved (or cleared) for that indication. There are two scenarios where the guidance contemplates approval of a new therapeutic product or indication prior to approval or clearance of a companion diagnostic: (1) the therapeutic is intended to treat a "serious or life-threatening condition for

[2] Petition of the American Clinical Laboratory Association, Docket No. FDA-20130P-0667 (Jun. 4, 2013); Petition of Genentech, Inc., Docket No. FDA-2008-P-0638 (Dec. 5, 2008); Petition of the Washington Legal Foundation (WLF), Docket No. FDA-2006-P-0149 (Sept. 28, 2006).

which no satisfactory alternative treatment exists," and (2) the labeling of an approved therapeutic needs to be updated to address a "serious safety issue" by indicating use with an IVD companion diagnostic.

Approval Pathways. FDA will determine the regulatory pathway for IVD companion diagnostic devices using the same risk-based criteria it applies to all medical devices. However, in a footnote, FDA states that "most IVD companion diagnostic devices will be Class III devices[.]" The guidance further clarifies that FDA does not expect most therapeutic-companion diagnostic pairs to meet the definition of combination products, though the agency intends to require separate marketing applications for the therapeutic product and diagnostic regardless of whether the products could constitute a combination product.

Labeling. The guidance briefly addresses the labeling of in vitro companion diagnostic devices and their corresponding therapeutic products. Ordinarily, information about the use of an IVD companion diagnostic device must be included in the therapeutic product's labeling. Likewise, an IVD companion diagnostic device must be cross-labeled for use with the therapeutic product for which it has been approved or cleared for use.

Investigational Use. IVD companion diagnostic devices used in clinical trials to make critical treatment decisions, such as patient selection or treatment assignment, will be considered significant risk devices, and the device sponsor will be required to comply with investigational device exemption (IDE) requirements. If a diagnostic device and a therapeutic product are to be studied together to support their respective approvals, both products can be studied in the same investigational study, if the study is conducted in a manner that meets both the requirements of the IDE regulations and the investigational new drug (IND) regulations.

Connection with Proposed LDT Framework. Although the final guidance reflects few changes from the 2011 draft guidance, the release of the final guidance on the same day FDA released its proposed LDT framework provides important additional context. Under the proposed LDT regulatory framework, LDTs serving as companion diagnostics would eventually be required to go through the PMA approval or 510(k) clearance process in accordance with the policies outlined in FDA's companion diagnostic guidance.

Notably, the companion diagnostic guidance and LDT framework provide an opening for the use of unapproved LDTs as companion diagnostics in some contexts. Specifically, unapproved LDTs could still be used to support therapeutic product approval in cases that fall under the two exceptions to concurrent approval: (1) therapeutics intended to treat a "serious or life-threatening condition for which no satisfactory alternative treatment exists," and (2) approved therapeutics seeking a new indication for use with a companion diagnostic to address a "serious safety issue." This is because the proposed LDT regulatory framework provides for continued enforcement discretion with regard to premarket review requirements for LDTs for "rare diseases" and LDTs serving unmet medical needs.

Ropes & Gray will continue to monitor developments in this area. If you have any questions, please contact any member of Ropes & Gray's FDA regulatory practice or your usual Ropes & Gray Advisor.