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COMMENTARY

FDA Releases Framework for Overseeing Laboratory Developed Tests

On September 30, 2014, the U.S. Food and Drug Administration ("FDA") released the two draft guidance documents setting forth FDA's proposed framework for regulating Laboratory Developed Tests ("LDTs") as medical devices[1]: (i) *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Oversight of Laboratory Developed Tests (LDTs)* (the "draft *Framework*")[2]; and (ii) *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)* (the "draft *Notification Guidance*"). These draft guidances are nearly identical to the preliminary versions of the documents labeled "Anticipated Details" that FDA submitted to Congress on July 31, 2014, as required by Section 1143 of the Food and Drug Administration Safety and Improvement Act of 2012.[3] Ultimately FDA intends to end its policy of enforcement discretion toward LDTs but will not regulate LDTs unless or until at least one of the draft guidance documents is finalized. Enforcement discretion for LDTs will gradually disappear over the next decade, as FDA implements any final *Framework*, based on the draft guidance.

FDA proposes applying its existing risk-based system for regulating other medical devices to most LDTs. More specifically, most LDTs would be classified into the three existing device classes based on whether they are low (Class I), moderate (Class II), or high (Class III) risk. LDTs FDA has already cleared or approved will retain their existing device classifications. However, FDA's draft *Framework* for regulating LDTs has effectively expanded the system by creating categories of LDTs that would be regulated first because they present the highest risk or be subject to minimal regulation to ensure availability or because they present the lowest level of risk.

FDA's proposed application of the draft *Framework* to LDTs would occur in multiple steps. First, most laboratories would be subject to additional requirements for reporting adverse events to FDA. Second, LDT laboratories would be required to submit descriptive information about their LDTs to FDA. Third, FDA, with Advisory Committee input, would classify each existing type of LDT based on any submitted adverse events and descriptive information. Fourth, FDA would create priority lists for Class III and Class II devices based on their comparative level of risk within each class. Finally, LDTs would be required to comply with the premarket and postmarket requirements that FDA has specified apply to the three classes and two categories of LDTs. FDA would start by regulating the

highest-risk LDTs followed sequentially by Class III, Class II, Class I, and finally the lowest-risk devices. Thus, FDA would gradually phase out the exercise of enforcement discretion for LDTs. FDA would, however, retain the authority to decrease or increase the implementation time and/or scope of the regulatory requirements for certain types of LDTs based on factors such as their scarcity or additional risk information.

FDA's explanation for the Agency's shift in policy and a more detailed description of FDA's proposed regulatory framework for LDTs appear below. A tabular summary of the draft *Framework* is available here. FDA's timeline for regulating LDTs is available here.

The History of LDTs and FDA's Changing Views on LDT Regulation

The draft *Framework* describes the history of LDTs and FDA perspective on the historical reasons for its exercise of enforcement discretion. Following passage of the Medical Device Amendment, when FDA began actively regulating medical devices in 1976, LDTs generally had the following characteristics: (i) local laboratories manufactured small volumes of LDTs that were similar to well-characterized, standard diagnostic devices; (ii) laboratory personnel performed the testing using manual techniques; (iii) the laboratories were located in the same institutions where the physicians and pathologists were caring for the patients whose tests results they interpreted; and (iv) the laboratories manufactured these LDTs using components legally marketed for clinical use. FDA's position is that LDTs met the definition of "medical devices" at that time (1976) in that they are used to diagnose conditions but that the Agency decided not to regulate them because they were low risk.

The draft *Framework* further describes changes to laboratories and the use of LDTs over time. Today, many laboratories that manufacture LDTs are independent of the facilities in which the patients are receiving care, and they are often the only tool available for diagnosing the condition of interest. Modern LDTs rely more on instrumentation and software to perform the test and/or interpret results. Further, worldwide overnight shipping and new modes for transmitting information have increased the volume of tests performed and the physical distance between the health care provider/patient and the laboratory. Based on the evolution of LDTs over the last few decades, FDA has now concluded that LDTs have become more like commercially available *in vitro* diagnostic devices,[4] which the Agency has regulated for more than 35 years.

Although LDTs already must comply with the Clinical Laboratory Improvements Amendments ("CLIA"),[5] administered by the Centers for Medicare and Medicaid Services ("CMS"), FDA now believes these regulations are insufficient to ensure public safety. For example, FDA points out that the Medicaid regulations do not require premarket review, adverse event reporting, or removal of unsafe devices from the market. The draft *Framework* references LDTs for Infectious Agents (donor screening tests) used in Blood and Blood Components and Human Cellular and Tissue Products. These are already subject to FDA's regulatory requirements for devices, including registration, listing, medical device reporting, premarket review, and Quality System regulations through the Office of Blood Research and Review in the Center for Biologics Evaluation and Research ("CBER"). Thus, FDA already regulates them. Notwithstanding this example, FDA has proposed to continue the exercise of enforcement discretion with respect to all device requirements for certain types of LDTs: (i) LDTs used only for law enforcement purposes, and (ii) certain LDTs used to determine histocompatibility for transplanted organs and tissue. Accordingly, FDA's position under the draft *Framework* would regulate different types of LDTs differently based primarily on the level of risk they present.

FDA's Information Collection Regarding LDTs

In order to develop a risk-based system for regulating LDTs, FDA needs to understand the number and types of LDTs that laboratories are currently using and the risks they present.

LDT Notification

FDA has proposed that each laboratory that manufactures only LDTs identify and describe its LDTs to the Agency within six months after publication of the final *Framework*. FDA also proposes that laboratories submit LDT notification prior to initial clinical use for LDTs introduced at least six months after publication of the final *Framework* and when they significantly

change an LDT's intended use. FDA does not expect LDT notification from laboratories that manufacture any device other than an LDT, LDTs that FDA currently regulates (i.e., screening test for donated blood, blood components, and tissue products), and cleared or approved LDTs since they should already comply with FDA's device establishment registration and device listing requirements in 21 C.F.R. Part 807, and thus, the Agency should already have information about them. FDA also does not expect LDT notifications for LDTs the Agency will not regulate even if it finalizes the draft *Framework*, i.e., LDTs used solely for law enforcement purposes or LDTs used in CLIA-certified, high-complexity histocompatibility laboratories for transplantation of organs stem cells and tissues (excluding LDTs used in HLA testing for blood transfusion).

FDA proposes that LDT notification include the following information:

- The name and contact information for the laboratory;
- The name of the test;
- The monthly test volume;
- The intended and clinical uses of the test;
- The analyte or other substance that the test measures;
- The disease or condition for which the LDT is indicated;
- The intended patient population, including whether the LDT would be used on patients under 21;
- The sample type;
- The test method; and
- A statement whether the LDT is a modification to an already-cleared or approved test, and, if so, a description of the modification(s).

FDA also expects laboratories to update LDT notifications when they make significant changes to an LDT, other than changes to indications.

If a laboratory does not submit an LDT notification for each LDT for which FDA has called for such notifications by the applicable deadline, FDA would require the laboratory to register as a device establishment and list its LDTs under a product code specifically for LDTs immediately after that deadline. As explained in more detail below, many laboratories could postpone, but not avoid, registering as device establishments and listing LDTs by submitting timely LDT notifications.

Medical Device Reports

Under 21 C.F.R. Part 803, Subpart E, FDA proposes requiring laboratories that manufacture LDTs to submit medical device reports ("MDRs") within 30 days regarding deaths and serious injuries if their LDTs reasonably caused or contributed to the adverse event, as well as malfunctions of the LDTs or similar devices that would likely cause or contribute to deaths or serious injuries if they were to recur. According to the draft *Framework*, FDA's MDR requirements for user facilities already apply to laboratories that use LDTs. Thus, they must submit MDRs for LDT-related deaths to FDA and the manufacturer, and MDRs for LDT-related serious injuries to the manufacturer of the LDT, if known, within 10 working days of becoming aware of a reportable event under 21 C.F.R. Part 803, Subpart D. This information would help FDA identify and evaluate LDT risks.

FDA's Proposed Classification or Categorization of LDTs

In general, FDA would classify most LDTs as Class I if they present a low risk, Class II if they present a moderate risk, and Class III if they present a high risk. FDA would also create priority lists for regulating Class III and Class II LDTs in descending order of risk compared to other LDTs in that class. FDA states the following LDTs are likely to be highest-priority Class III LDTs: (i) devices that act like companion diagnostics; (ii) screening devices for serious diseases and/or conditions without any available confirmatory diagnostic product or procedure; and (iii) diagnostic devices for certain infectious diseases with high-risk intended uses. An Advisory Committee will make recommendations to FDA regarding the classification and prioritization of LDTs.

As noted above, FDA has identified certain categories of LDTs for which FDA's regulation would not be based on their classification. FDA has identified the following categories as the "highest-risk" LDT, which the Agency would regulate first: (i) LDTs with the same intended use as cleared or approved companion-diagnostics;[6] (ii) LDTs with the same intended use as approved Class III medical devices; and (iii) certain LDTs used to determine the safety/efficacy of blood or blood products, most of which CBER regulates. On the other hand, the following three categories of LDTs would be subject to minimal regulation: (i) LDTs for Rare Diseases;[7] (ii) Traditional LDTs;[8] and (iii) LDTs for Unmet Needs.[9]

Proposed Requirements Based on LDT Classification/Categorization

FDA proposed the following premarket and postmarket requirements for each class/category of LDTs and the time frames for their implementation. FDA noted that other device requirements might also apply to LDTs.

Device Establishment Registration and Listing

FDA would require laboratories that submitted timely LDT notifications for their highest risk, Class III, or Class II LDTs to register as device establishments upon submitting an initial premarket submission for the product. FDA requires device manufacturers to pay an annual user fee ($3,646 for October 1, 2014, to September 30, 2015) to register their establishments. Class I LDTs would not have to register as a device establishment or list their device. FDA would require laboratories to list their LDTs as devices when they send the first premarket submission for that product.

Premarket Review

FDA has proposed the following premarket review requirements for LDTs:

- **Highest-Risk:** Require the submission of premarket approval applications ("PMA") or 510(k) premarket notifications within 12 months of the publication of the final *Framework* for any LDT marketed at that time.
- **Class III LDTs:** Require the submission of PMAs sequentially by type based on the Class III priority list starting 36 months after publication of the *Framework* (assuming FDA issues the priority list within 24 months of that publication). FDA expects to complete the review of Class III LDTs within five years after final publication of the *Framework*.
- **Class II LDTs:** Require the submission of 510(k) notices sequentially by type based on the Class II Priority List after the phased-in period for the PMA review of Class III devices. Third parties would review most 510(k) notices for LDTs. FDA expects to complete review of 510(k) notices for Class II LDTs within nine years after publication of the final *Framework*.

FDA would require premarket submission before initial clinical use for *new* Highest-Risk, Class III, and Class II LDTs. Class I LDTs would not require 510(k) clearance or PMA approval. FDA would continue to exercise enforcement discretion and not require premarket submission for minimally regulated LDTs with one exception: FDA would require a premarket submission for an LDT for an Unmet Need within 12 months if FDA clears or approves a device for the same indication.

Compliance with Quality System Regulations

FDA would require laboratories to comply with FDA's Quality System Regulations in 21 C.F.R. Part 814 when: (i) submitting a PMA for a Highest-Risk or Class III LDT; or (ii) a 510(k) notice is cleared for a Highest-Risk or a Class II LDT unless it was previously 510(k) exempt. Class I LDTs would continue to be subject to enforcement discretion with respect to Quality Systems Regulations ("QSRs"). It is not clear whether FDA would continue to exercise enforcement discretion and not require compliance with QSRs for any of the minimally regulated LDTs.

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The draft guidances are a major step toward FDA's regulation of LDTs and, if finalized as drafted, would significantly expand the types of products FDA regulates as devices. FDA estimates it will take nine years to implement the proposed regulation, but LDTs that FDA decides are highest risk will be subject to premarket review within the first year of the process. **Comments on the draft LDT guidances are due on January 30, 2015.** We urge you to review the draft guidance documents and consider submitting comments on these draft guidance documents, given their potentially significant impact on the clinical use of LDTs.

Note: FDA will hold a public webinar regarding the draft guidance documents to answer questions on October 23, 2014, at 2:00 p.m. EST. The CDC and CMS will also host a public workshop to discuss the *Framework* on November 4–5, 2014, in Atlanta, Georgia (also available via webinar).

Lawyer Contacts

For further information, please contact your principal Firm representative or one of the lawyers listed below. General email messages may be sent using our "Contact Us" form, which can be found at www.jonesday.com.

Laurie A. Clarke
Washington
+1.202.879.3498
lclarke@jonesday.com

Colleen M. Heisey
Washington
+1.202.879.3449
cmheisey@jonesday.com

Brigid C. DeCoursey
Washington
+1.202.879.3651
bdecoursey@jonesday.com

Endnotes

1 As described by FDA, an LDT is a type of *in vitro* diagnostic test that is intended for clinical use and designed, manufactured, and used within a single laboratory. LDTs do not include devices designed or manufactured completely, or partly, outside of the laboratory that offers and uses them. LDTs were formerly called "home brews" and/or "in-house devices." The draft *Framework* and draft *Notification Guidance* apply to products marketed as LDTs, regardless of whether the products meet the definition. However, they do not apply to direct-to-consumer LDTs.

2 The draft *Framework* appears to apply only to high-complexity CLIA-certified laboratories, as defined in 42 C.F.R. § 493.55.

3 Pub. L. No. 112-144, 126 Stat. 993 (2012).

4 IVDs are tests that can detect diseases, conditions, or infections. Some tests are used in laboratory or other health professional settings, and other tests are for consumers to use at home.

5 42 U.S.C. § 263a.

6 A companion diagnostic device is an *in vitro* diagnostic device that provides information essential for the safe and effective use of a corresponding therapeutic product; the instructions for use for both the companion diagnostic and therapeutic product, as well as any generic equivalents, stipulate their combined use.

7 LDTs for Rare Diseases must meet the criteria for Humanitarian Use Devices in 21 C.F.R. § 814.102 , i.e., fewer than 4,000 persons in the United States would be diagnosed using the LDT per year.

8 FDA intends to determine whether an IVD is a traditional LDT based on whether: (i) the device meets the Framework's definition of an "LDT," i.e., whether the device is designed, manufactured, and used by a single laboratory; (ii) the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient who is being diagnosed and/or treated at the same facility or within the facility's health care system; (iii) the LDT comprises only legally marketed components and instruments, e.g., analyte specific reagents (21 C.F.R. § 864.4020), general purpose reagents (21 C.F.R. § 864.4010), and various classified instruments; and (iv) the LDT is interpreted by qualified laboratory professionals without the use of automated instrumentation or software.

9 FDA intends to determine whether an IVD is an LDT for Unmet Needs based on whether: (i) the device meets the definition of "LDT" in this guidance, i.e., it is a device designed, manufactured, and used by a single laboratory; (ii) any FDA cleared or approved IVD for that specific intended use is available; and (iii) the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient who is being diagnosed and/or treated at the same health care facility or within that facility's health care system.