FDA’s Risk-Based Laboratory Developed Tests Proposal Would Transform the Regulation of Diagnostic Testing in the U.S.

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On July 31, 2014, the U.S. Food and Drug Administration’s (FDA or Agency) Center for Devices and Radiological Health (CDRH) provided notification to Congress¹ regarding the Center’s intent to issue draft guidance entitled Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) (Framework Document). CDRH has provided the Framework Document as required by Section 1143 of the Food and Drug Administration Safety and Innovation Act (FDASIA), which required FDA to make a notification to Congress at least 60 days prior to issuing a draft or final guidance on the regulation of laboratory developed tests (LDTs).² Although not technically a proposed policy at this point, the Framework Document serves as FDA’s first attempt to regulate LDTs in a comprehensive manner since FDA was given explicit authority of diagnostic tests over 35 years ago.

As a result of the congressional notification requirement, FDA cannot publish draft guidance documents on this topic or establish a docket for public comments until at least 60 days after the notification. Thus, comments on the Framework Document will not be eligible for submission until sometime in late September or early October 2014. In the meantime, the diagnostic industry, patients and Congress should interpret this document as FDA’s vision of where the regulation of LDTs is (or should be) headed in the future.

FDA’s Framework Document describes a risk-based framework for addressing the regulatory oversight of a subset of in vitro diagnostic devices (IVDs) referred to as LDTs. The Framework Document narrowly

¹ The notice was provided to the Senate Committee on Health, Education, Labor & Pensions (HELP) and the House Committee on Energy and Commerce. See http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407409.pdf [hereafter Framework Document].

² In the past, LDTs were referred to as “home brew” or “in-house” devices. The term “laboratory developed test” and its acronym “LDT” replaced “home brew” over time, but the regulatory considerations are not affected by the change in terminology.
defines LDTs as a subset of IVDs that are intended for clinical use and designed, manufactured and used within a single laboratory.\(^3\) FDA provided the following example of an LDT:

A laboratory uses peer reviewed articles to guide development of a new diagnostic device. The laboratory uses general purpose reagents and analyze specific reagents combined with general laboratory instruments and develops a testing protocol, that together constitute a test system which is then verified and validated within the laboratory. Once validated this device is used by the laboratory to provide clinical diagnostic results.

While FDA’s narrow definition of an LDT excludes devices that are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them, FDA recognizes that some laboratories have relied on a more expansive definition and are currently providing tests identified as LDTs that incorporate design and manufacturing elements that reach beyond the walls of the individual laboratory performing the test. FDA’s formal position on these devices is that they were never intended to, and do not currently fall within the scope of the Agency’s existing LDT policy. FDA believes that LDTs in this category are technically out of compliance with the Federal Food, Drug, and Cosmetic Act (FDCA). However, as articulated in the Framework Document, FDA does intend to apply the same risk-based framework to all IVDs offered by CLIA-certified labs as LDTs, including those that fall outside of FDA’s narrow LDT definition. In other words, the policy articulated in the Framework Document applies to LDTs as defined by the labs themselves, not just FDA’s narrow subset of devices claiming LDT status.

The Framework Document is intended to provide guidance to clinical laboratories that offer LDTs about how FDA intends to enforce authorities that apply to such laboratories as medical device manufacturers\(^4\) under the FDCA or subject to Section 351 of the Public Health Service Act.

I. **Background on LDTs**

In 1976, Congress enacted the Medical Device Amendments, which amended the FDCA to create a comprehensive system for the regulation of medical devices intended for use in humans. Congress

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\(^3\) FDA generally does not exercise enforcement discretion for direct-to-consumer (DTC) tests regardless of whether they meet the definition of an LDT provided in this guidance. Therefore, the enforcement policies in this guidance do not apply to DTC tests, and FDA’s usual enforcement policies apply to DTC tests.

\(^4\) A manufacturer is any person who engages in the “manufacture, preparation, propagation, compounding, assembly, or processing of a device,” defined as “the making by chemical, physical, biological, or other procedures of any article that meets the definition of device in section 201(h)” of the FDCA. 21 C.F.R. § 807.3(d); see also 21 C.F.R. § 803.3.
defined “device”\(^5\) to encompass IVDs,\(^6\) with the definition applying equally to IVDs manufactured by conventional device manufacturers and those manufactured by laboratories (i.e., LDTs). While an IVD does meet the device definition—regardless of where or who manufactured it—FDA has generally exercised enforcement discretion since 1976 with respect to its oversight of LDTs.

The Centers for Medicare & Medicaid Services (CMS) began regulating laboratories, including those that develop LDTs, under the 1988 Clinical Laboratory Improvement Amendments (CLIA) (42 U.S.C. § 263a). CLIA governs the accreditation, inspection and certification process for laboratories, as well as a laboratories testing process (e.g., ability to perform accurate and reliable laboratory testing). However, accrediting bodies under CLIA do not evaluate test validation prior to marketing nor do they assess the clinical validity of a LDT (i.e., the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient). Thus, while CLIA oversight has played an important role in ensuring clinical labs are operating appropriately, it has not necessarily ensured that LDTs are properly designed, consistently manufactured, and are safe and effective for patients.

II. FDA Identified Gaps in Regulatory Oversight of LDTs

In 1976, FDA exercised enforcement discretion over LDTs in part because this subset of IVDs were used in a “traditional” manner, meaning: (1) LDTs were manufactured in small volumes in local labs; (2) LDTs were similar to well-characterized, standard diagnostic devices; (3) LDTs were intended for use in the diagnosis of rare diseases or for others to meet the needs of a local population; (4) LDTs tended to rely on manual techniques by lab personnel; (5) LDTs were typically used and interpreted directly by physicians and pathologists working within a single institution that was responsible for the patient; and (6) LDTs were manufactured using components\(^7\) that were legally marketed for clinical use.

According to FDA, since 1976 the LDT industry “has grown and evolved in significant ways.” For example, today LDTs: (1) are often used in laboratories that are independent of the healthcare delivery

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\(^5\) See Section 201(h) of the FDCA, defining “device” to include “… in vitro reagent, … .”

\(^6\) FDA regulations define IVDs as “those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h)’ of the FDCA, and may also be biological products. 21 C.F.R. § 809.3.

\(^7\) For purposes of this guidance, FDA explained that components that are legally marketed for clinical use refer to general purpose reagents, immunohistochemical stains, and other components marketed in compliance with applicable FDA regulatory requirements, e.g., properly labeled for in vitro diagnostic use (21 C.F.R. § 809.10(a)(4)) and manufactured in compliance with quality system requirements (21 C.F.R. Part 820).
entity; (2) are frequently manufactured with components and instruments that are not legally marketed for clinical use; (3) rely more heavily on high-tech instrumentation and software to generate results and clinical interpretations; and (4) are used more frequently given the advances in diagnostic devices that guide critical clinical management decisions for high-risk diseases and conditions, particularly in the context of personalized medicine. Based on the significant shift in the type of LDTs developed today, FDA determined that the attributes of modern LDTs create potential increased risk for patients in the absence of appropriate oversight.

FDA expressed “serious concern[] regarding the lack of independent review of the evidence of clinical validity of LDTs.”\(^8\) FDA explained that clinical validity, which is not evaluated under CLIA regulations, “is the ability of a diagnostic device to measure or detect the clinical condition for which the device is intended.”\(^9\) Because LDTs have not been properly clinically validated for their intended use\(^10\) and are used to make critical clinical decisions, FDA believes that such products could “potentially put patients at risk of missed or incorrect diagnosis,” which may cause a patient’s physician to fail to administer appropriate treatment or administer potentially harmful treatment with no benefit. In addition, CLIA oversight is not designed to ensure that LDTs are appropriately analytically validated for their intended use before the test is used clinically. Accordingly, FDA no longer believes a blanket enforcement discretion policy towards LDTs is appropriate.

III. Proposed LDT Framework

To address these concerns, FDA’s Framework Document proposes a strategy that would require manufacturers of a risk-identified subset of LDTs to notify FDA that they are developing LDTs, report significant adverse events to FDA, obtain appropriate pre-market review from FDA, and adhere to Quality System Regulation/Medical Device Good Manufacturing Practices (GMP) requirements.

A. LDT Framework: Risk-Based Classification of LDTs and Associated Regulatory Controls

FDA will rely upon the existing medical device classification system (e.g., Class I-III) to evaluate the risk of a particular type of LDT, and when appropriate, will use expert advisory panels to help classify devices not previously classified by FDA. FDA believes that the risks to health associated with LDTs, as with all

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\(^8\) Framework Document at 8.

\(^9\) Id.

\(^10\) “Intended use” refers to the objective intent of the persons legally responsible for the labeling of the device. The intent is determined by their expressions or may be shown by the circumstances surrounding the distribution of the device. 21 C.F.R. § 801.4.
In determining the risk an LDT poses to the patient and/or the user, and ultimately the regulatory strategy appropriate for an individual LDT type, FDA will 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; and
- Number and type of adverse events associated with the device, etc.

To provide additional clarity, FDA intends to issue draft guidance to describe what the Agency considers generally to be Class I, II or III LDTs within 18 months of finalization of the Framework Guidance. FDA expects that manufacturers with FDA approved or cleared LDTs will continue to comply with applicable regulations.\textsuperscript{11}

1. LDTs for which FDA does not intend to modify its enforcement discretion policy

For the following LDT types, FDA does not intend to enforce any new regulatory controls:

- LDTs used solely for forensic (law enforcement) purposes;
- Certain LDTs for transplantation when used in CLIA-certified, high-complexity histocompatibility laboratories when those LDTs are used in connection with organ, stem cell, and tissue transplantation:
  - to perform high resolution allele typing;
  - for antibody screening and monitoring; or
  - for the purpose of conducting real and “virtual” crossmatch tests.

As proposed, FDA will not enforce any regulatory requirements for LDTs in this category.

\textsuperscript{11} Manufacturers of tests that are used solely for in-process quality control testing in the manufacture of FDA-regulated articles should consult with FDA to determine applicable regulatory requirements.
2. LDTs for which FDA expects to receive notification of LDTs manufactured and enforce adverse event reporting requirements

For the LDT types identified below, FDA expects laboratories that manufacture, prepare, propagate, compound, assemble or process\textsuperscript{12} one or more of these LDTs to:

1. Notify FDA that they are manufacturing LDTs and provide basic information regarding each of these LDTs; and
2. Comply with the manufacturer reporting requirements of the MDR regulation (21 C.F.R. Part 803 Subpart E).

If LDT manufacturers comply with these requirements, FDA intends to continue to exercise enforcement discretion for applicable premarket review (510(k) or PMA) requirements and Quality System Regulation/Medical Device GMP requirements (21 C.F.R. Part 820). For these devices, FDA plans to enforce all other applicable medical device regulatory requirements.\textsuperscript{13} FDA plans to begin enforcing these requirements 6 months after publication of a final Framework Document.

LDT types for which FDA expects to receive notification from manufacturers and enforce adverse event reporting requirements include:

- **Low-risk LDTs.**
  - FDA defines low-risk LDTs as all Class I LDTs;
- **LDTs for rare diseases.**
  - FDA defines LDTs for rare diseases as LDTs developed to diagnose or to help diagnose a disease or condition with an incidence of fewer than 4,000 patients per year.
- **“Traditional LDTs.”**
  - FDA defines “Traditional LDTs” as IVD devices that reflect the types of LDTs available when FDA began its enforcement discretion policy in 1976.\textsuperscript{14}

\textsuperscript{12} For purposes of this advisory and FDA’s Framework Document, “manufacture” is used to encompass all of these terms.

\textsuperscript{13} Unless otherwise exempted, general controls are applicable to all medical devices regardless of their classification. General controls include, but are not limited to, the provisions of the FDCA pertaining to prohibitions on adulteration and misbranding, establishment registration and device listing, premarket notification, banned devices, compliance with certain remedies required through an order issued under section 518 of the FDCA (e.g., notification, repair, replacement and refund), records and reports, restricted devices, and good manufacturing practices. Section 513(a)(1)(A) of the FDCA (21 U.S.C. § 360c(a)(1)(A)).

\textsuperscript{14} FDA’s Framework Document provides a list of factors FDA will consider when identifying “Traditional LDTs.”
- “LDTs for Unmet Needs,” when no FDA-approved or cleared equivalent device is available.
  - FDA has not provided an explicit definition for “LDTs for Unmet Needs” but does provide a list of factors the Agency will consider when identifying such devices. However, no “LDTs for Unmet Needs” can have the same specific intended use of an FDA cleared or approved LDT. Clearance or approval of an LDT with the same specific intended use removes the “LDTs for Unmet Needs” designation for all other LDTs with that specific intended use.

3. **LDTs for which FDA intends to enforce premarket review requirements, the Quality Systems Regulation, notification of LDTs manufactured and adverse event reporting requirements**

For the LDT types identified below, FDA expects laboratories that manufacture one or more of these LDTs to comply with:

1. Premarket review requirements (510(k) or PMA depending on the classification of the LDT);
2. Quality System Regulation/Medical Device GMP requirements (21 C.F.R. Part 820);
3. Registration and listing requirements (21 C.F.R. Part 807) with the option to provide notification of LDTs manufactured; and

For these devices, FDA plans to enforce all other applicable medical device regulatory requirements. FDA states that it will begin enforcing the notification and MDR requirements 6 months after publication of a final Framework Document and phase in the remaining requirements over a nine-year period starting from the publication that document.

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15 Unless otherwise exempted, general controls are applicable to all medical devices regardless of their classification. General controls include, but are not limited to, the provisions of the FDCA pertaining to prohibitions on adulteration and misbranding, establishment registration and device listing, premarket notification, banned devices, compliance with certain remedies required through an order issued under section 518 of the FDCA (e.g., notification, repair, replacement and refund), records and reports, restricted devices and good manufacturing practices. Section 513(a)(1)(A) of the FDCA (21 U.S.C. § 360c(a)(1)(A)).
LDT types for which FDA intends to enforce premarket review requirements, the Quality Systems Regulation, notification of LDTs manufactured, and adverse event reporting requirements include:

- High-risk LDTs
  - Highest Risk LDTs
    - LDTs with the same intended use as a cleared or approved companion diagnostic;
    - LDTs with the same intended use as an FDA-approved Class III medical device; and
    - Certain LDTs for determining the safety or efficacy of blood or blood products.
  - Other Class III LTDs.
- Moderate-risk LDTs
  - FDA defines moderate-risk LDTs as all Class II LDTs.

**Anticipated* Timeline for Implementation of FDA’s Proposed LDT Policy**

- **July 31, 2014** - FDA issues Framework Document as a notification of proposed policy to Congress
- **October 2014** - FDA issues Draft LDT Framework Guidance with 90-day comment period.
- **January 2015** - Comment period on Draft Framework Guidance closes
- **January 2016** - FDA issues Final Framework Guidance
- **July 2016** - FDA begins enforcing LDT notification and MDR reporting requirements for all FDA regulated LDTs
- **January 2017** - FDA begins enforcing premarket review and QSR requirements for the highest-risk LDTs
- **2018** - FDA announces the priority list for the remaining Class III LDTs phasing in premarket review and QSR requirements
- **2019 through 2021** - Phased-in enforcement of premarket review and QSR requirements for Class III LTDs
- **2020** - FDA announces the priority list for the remaining Class II LDTs phasing in premarket review and QSR requirements
- **2021 through 2025** - Phased-in enforcement of premarket review and QSR requirements for Class II LTDs

*Based on the most aggressive timeline estimates proposed by FDA.
B. LDT Framework: Summary of Regulatory Controls and Associated Timelines Applicable to Certain LDT types

1. MDR Requirements

With the exception of forensic LDTs and certain LDTs used in connection with transplantation, FDA intends to enforce the manufacturer reporting requirements of the MDR regulation for laboratories manufacturing all LDT types. The MDR regulation requires the manufacturer of a medical device to submit reports to the FDA whenever they become aware\(^\text{16}\) of information that reasonably suggests that a device they market may have caused or contributed to\(^\text{17}\) a death or serious injury, or has malfunctioned and the malfunction would be likely to cause or contribute to a reportable death or serious injury should it recur.\(^\text{18}\)

For all categories of LDTs for which FDA has identified an intent to require compliance with the MDR requirements, FDA intends to begin enforcing those requirements six months after publication of a final LDT framework guidance. Manufacturers of LDTs should notify FDA if they are developing LDTs and must begin to report significant adverse events to FDA so that problems can be detected and corrected in a timely manner.\(^\text{19}\)

The MDR regulation provides a mechanism for FDA to identify and monitor significant adverse events involving LDTs that may not currently be on FDA’s radar. By enforcing the MDR requirements early and consistently across all LDT types, it can be assumed that adverse event information gathered will be utilized in the risk based classification most moderate-risk and high-risk LDTs will eventually undergo.

2. Notification Requirements

\(^{16}\) A manufacturer has “become aware” of an event when an employee of the entity required to report has acquired information to reasonably suggest a reportable adverse event has occurred. 21 C.F.R. § 803.3.

\(^{17}\) The term “caused or contributed to” means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, malfunction, improper or inadequate design, manufacture, labeling, or user error. 21 C.F.R., § 803.3.

\(^{18}\) 21 C.F.R. § 803.50.

\(^{19}\) In its Notification to Congress, FDA also issued a second document, FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs), which explains what MDR procedures LDT manufacturers should develop and what adverse events to report, and clarifies important terminology in the context of LDT manufacturers and user facilities with respect to MDRs.
With the exception of forensic LDTs and certain LDTs used in connection with transplantation, FDA intends to enforce a notification requirement for laboratories manufacturing one or more LDTs. Under the proposal, labs must notify FDA that they are manufacturing LDTs and provide basic information regarding each of these LDTs. This notification requirement is similar but less stringent than the registration and listing requirements applicable to all other medical devices. Laboratories that do not notify FDA that they are manufacturing LDTs or provide basic information regarding each of the LDTs manufactured in their laboratory within the abovementioned timeframes will fall within the Agency’s normal enforcement approach with respect to the registration and listing requirements for all medical devices (21 C.F.R. Part 807). Because the notification process is separate and distinct from the establishment registration and device listing requirements of the FDCA, laboratories are not required to submit registration fees to FDA with the notification.

For all LDT types for which FDA has identified an intent to require notification of LDTs manufactured or compliance with the registration and listing requirements, FDA intends to begin enforcing those requirements six months after publication of a final LDT framework guidance.

3. Premarket Review Requirements

For high-risk and moderate-risk LDTs, FDA believes a policy of continued enforcement discretion concerning applicable pre-market review requirements is no longer appropriate. Thus, for all LDTs that do not meet FDA’s definition of forensic LDTs, certain LDTs used in connection with transplantation, low-risk LDTs, LDTs for rare diseases, “Traditional LDTs,” and “LDTs for Unmet Needs,” FDA intends to phase in the enforcement of applicable premarket requirements based upon the risk associated with that device. FDA plans to focus its efforts on the highest risk devices first and gradually phase in enforcement for other devices over time.

a. Premarket Review for Highest Risk LDTs, Including Companion Diagnostics

FDA believes that the “highest risk devices” identified in the Framework Document as a subset of high-risk LDTs are among the most risky LDTs currently available on the market because the device is used in

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20 See id., which also explains the process and data elements required for clinical laboratories to notify FDA of the LDTs they manufacturer. Appendix A of that document provides FDA’s proposal on the data elements required in an LDT notification.

21 21 C.F.R. § 807.20(a). Submission of the registration and listing information must be accompanied by payment of the registration fee (Section 738(a)(3) of the FDCA (21 U.S.C. § 379j(a)(3))).
either direct patient therapy (Companion Diagnostic LDTs),\textsuperscript{22} for blood donor screening,\textsuperscript{23} or have the same intended use as a device that FDA has already reviewed and determined to be in the highest risk category, Class III. For this reason, FDA will prioritize its premarket review efforts on these LDT types.

For the highest risk LDTs already on the market, FDA intends to begin enforcing premarket review requirements (generally requiring an approved PMA) 12 months after publication of a final framework guidance. For these LDTs, FDA does not wish to interrupt patient access to diagnostic tests. Thus, FDA intends to extend its current premarket review enforcement discretion policy for high-risk devices for the immediate 12-month period after issuance of a final framework guidance and while the premarket submission is under review with FDA. For new high-risk LDT types (i.e., those that become available for patient testing after publication of a final Framework Document), FDA intends to begin enforcing premarket review requirements immediately and expects manufacturers to make an appropriate premarket submission and obtain approval or clearance prior to use.

b. Premarket Review of Other High-risk and Moderate-risk LDTs

For all other LDTs that do not meet the FDA criteria of a highest-risk LDT or fall within the LDT types excluded from pre-market review, as noted above, FDA intends to require the appropriate risk-based premarket submission (510(k) for Class II LDTs and PMA for Class III LDTs). For LDTs lacking an established device classification (LDTs with the same intended use as an FDA approved or cleared test),

\textsuperscript{22} In addition to the Framework Document, FDA also released Draft Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices, available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery. This guidance is intended to assist (1) sponsors who are planning to develop a therapeutic product (either a novel product or an existing product with a new indication) for which the use of an IVD companion diagnostic device (or test) is essential for the therapeutic product’s safe and effective use; and (2) sponsors planning to develop an IVD companion diagnostic device that is intended to be used with a corresponding therapeutic product. The guidance (i) defines \textit{in vitro companion diagnostic device}; (ii) explains the need for FDA oversight of IVD companion diagnostic devices; (iii) clarifies that, in most circumstances, an IVD companion diagnostic device and its corresponding therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling; (iv) provides guidance on possible premarket regulatory pathways and FDA’s regulatory enforcement policy; and (v) describes certain statutory and regulatory approval requirements relevant to therapeutic product labeling that stipulates concomitant use of an IVD companion diagnostic device when use of the IVD is essential to the safe and effective use of the therapeutic product.

\textsuperscript{23} For example, FDA considers devices used in determining the safety or efficacy of blood or blood products to be high-risk devices, including devices used for HLA testing for transfusion compatibility and those used for blood donor infectious disease supplemental or confirmatory testing, or for red blood cell compatibility testing (i.e., phenotyping and/or genotyping of donors and recipients or mother and fetus). FDA regulations require that blood donor screening testing be performed, and that the donor screening devices used be “approved for such use” and performed “in accordance with the manufacturer’s instructions.” 21 C.F.R. § 610.40(a), (b)).
FDA plans to analyze the data it collects through notification and publically prioritize the remaining device categories based on risk.

FDA expects to announce the priority list for the remaining Class III LDTs within 24 months after publication of a final LDT framework guidance. In the document announcing the priority list, FDA intends to describe the order in which it plans to enforce the LTD premarket review requirements. FDA intends to begin enforcing the premarket review requirements for those LTDs not captured in FDAs “highest risk” category but in the highest priority grouping no less than 12 months after the priority list is announced (approximately 36 months after publication of a final LDT framework guidance). FDA intends to complete the phased-in enforcement of premarket review requirements for Class III LTDs within five years after publication of a final LDT framework guidance.

FDA expects to announce the priority list for the remaining Class II LDTs within four years after publication of a final LDT framework guidance. FDA intends to begin the phased-in enforcement of premarket review requirements for Class II devices once it has completed phase-in of Class III devices. FDA anticipates completing the phased-in enforcement of premarket review requirements for Class II LTDs within nine years after publication of a final LDT framework guidance.

If a premarket submission is required for a particular LDT, FDA intends to continue to exercise enforcement discretion while the submission is under review. After FDA begins enforcing the premarket review requirements for LDTs in a particular category, FDA expects labs that develop new LDTs to make an appropriate premarket submission and obtain approval or clearance prior to use.

4. Quality System Regulation Requirements

For high-risk and moderate-risk LDTs, FDA believes a policy of continued enforcement discretion concerning enforcement of the Quality System Regulation (QSR)(21 C.F.R. Part 820), is no longer appropriate. Thus, for all LDTs that do not meet FDA’s definition of forensic LDT, certain LDTs used in connection with transplantation, low-risk LDTs, LDTs for rare diseases, “Traditional LDTs,” and “LDTs for Unmet Needs,” FDA intends to phase in the enforcement of applicable premarket requirements based upon the risk associated with that device.

FDA developed the QSR to define the minimal quality system requirements that medical device manufacturers must implement in order to assure that the finished device will be safe and effective. FDA intends to continue to exercise enforcement discretion with respect to QSR requirements until a manufacturer of a given LDT submits a PMA or FDA issues a 510(k) clearance order for the LDT. The clinical laboratory that manufactures and uses the LDT will be responsible for having a quality system in place that meets the minimum requirements in 21 C.F.R. Part 820, either at the time of PMA submission.
(the facility that makes the device must pass an inspection as a condition of PMA approval as a matter of law (21 C.F.R. § 814.45(a)(3))), or prior to market launch for cleared devices, as applicable. FDA encouraged laboratories developing new LDTs to begin working toward compliance with QSR requirements.

FDA recognized that there may currently be low-risk LDTs that, based upon intended use and technology, would be classified as Class I diagnostic devices that are not exempt from 510(k) submission requirements, or Class I or II diagnostic devices that are exempt from 510(k) submission requirements. FDA intends to continue exercising enforcement discretion with respect to QSR requirements for these LDTs at this time.

What is not clear, however, is whether specific guidance on QSR requirements as applicable to LDTs will be forthcoming from the Agency. Because many of the currently enforced CLIA requirements serve the same intended purpose as the QSR requirements, many in the LDT community see full implementation of QSR on LDT manufactures/labs as unnecessarily duplicative.

IV. Conclusion

Now that FDA has planted its flag in the ground regarding an initial LDT policy proposal, the LDT community is left to ponder what they can and should be doing to prepare for the potential change in landscape.

The most important thing to remember is that FDA’s proposal is just that, a proposal. The implications of Congress’s 2012 notification requirement should not be overlooked. While the political sensitivity of any issue is subject to change over any two-year period, the specific prohibition on FDA issuing a draft guidance on a given topic is highly uncommon. When viewed in this light, it is fair to assume that Members of Congress will be scrutinizing this proposal in the weeks to come. Dr. Alberto Gutierrez, Director of the CDRH Office responsible for regulating IVDs and one of the chief architects of FDA’s LDT proposal, was reported last year as explicitly referencing the statutory amendment as a means for Congress being given another chance to quash an attempt by FDA to regulate LDTs. “It seems to me that the only reason Congress wants to know 60 days before is because they have lobbyists who want to prevent the guidance from coming out,” Gutierrez told the American Association for Clinical Chemistry.24

For some, the next 60 days will be viewed as an opportunity to work with Congress to support or intervene on this issue. For most, however, the next two months will provide an opportunity to observe

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the strength and limitations this policy has politically. Even if the proposal is issued unchanged, the breadth of FDA’s proposed framework will be subject to close congressional oversight in the coming years, and ultimately the proposal may be significantly narrowed. If legislative changes do not occur sooner, the reauthorization of medical device user fees, which must occur by 2017, will provide a vehicle for a legislative battle over the issue.

A nuanced reading of the Framework Document reveals that FDA may not be putting all its eggs in this basket just yet. FDA’s decision to define LDT’s narrowly, but to still apply its proposed policy to the more expansive definition applied by many in the LDT industry may signal a back-up regulatory approach should the proposed framework fail to see implementation. By defining LDTs as a small slice of the currently unregulated laboratory diagnostic industry, FDA could be seen as preserving its ability to take enforcement action against diagnostic manufacturers who do not meet FDA’s narrow definition of an LDT without technically enforcing an LDT policy or departing from the 1976 policy as interpreted by FDA. Preventing FDA from developing or changing an existing policy is a familiar part of the administrative process for all FDA stakeholders, but preventing a federal executive agency from enforcing the laws already on its books is a more radical legislative step.

For the immediate future, it is important for LDT manufacturers to understand how FDA may classify the tests it develops and the proposed regulatory controls FDA would like to apply to those devices. By gaining a better understanding of how FDA views the tests that a company offers, that company is in a much better position to assess its options in responding to FDA’s proposal or for preparing to bring its lab(s) into compliance with the increased regulatory oversight from FDA.

*If you have any questions about any of the topics discussed in this advisory, please contact your Arnold & Porter attorney or any of the following attorneys:*

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