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FDA NOTIFIED CONGRESS OF ITS PLAN TO ISSUE DRAFT GUIDANCES DESCRIBING REGULATORY FRAMEWORK FOR LABORATORY DEVELOPED TESTS

On July 31, 2014, the Food and Drug Administration (FDA) notified Congress of its intent to issue two long-anticipated draft guidance documents that propose to implement a new framework for regulatory oversight of laboratory developed tests (LDTs).[1] FDA's notification is in the form of two documents entitled: "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" ("LDT Framework for Regulatory Oversight") and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)" ("LDT Notification and Reporting "). These two documents are hereafter referred to as the "LDT Framework Documents."

FDA announced over four years ago that it intended to change its oversight framework for LDTs and apply a risk-based approach to the regulation of LDTs under the medical device provisions of the Federal Food, Drug, and Cosmetic Act (FDCA).[2] Just prior to FDA's notification to Congress of the LDT Framework Documents, five U.S. Senators sent a letter, dated July 2, 2014, to the Office of Management and Budget (OMB), urging the OMB to release a draft guidance proposed by the FDA relating to the regulation of LDTs, which reportedly had been in front of OMB for several years.[3]

FDA was required by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) to provide notification to Congress at least 60 days prior to issuing any guidance on the regulation of LDTs. In FDA's notification to Congress, FDA stated that it would not publish the draft guidance documents or establish a docket for public comments until at least 60 days after the July 31 notification. Assuming FDA publishes the draft guidance documents as it has announced, it will then accept comments from the public.

As described more fully below, the LDT Framework Documents announce FDA's intent to implement a risk-based framework to require compliance with the medical device requirements of the FDCA for LDTs, as well as continued enforcement discretion for certain regulatory requirements and types of LDTs. The LDT Framework Documents also propose timelines for phased-in compliance.

Background

LDTs are developed for in-house use and are not commercially distributed to other laboratories. In contrast, commercially available *in vitro* diagnostic (IVDs) test kits are developed by diagnostic

[1] Notice from Sally Howard, Deputy Commissioner, Policy, Planning and Legislation, FDA to the Senate Committee on Health, Education, Labor and Pensions and the House Committee on Energy and Commerce (July 31, 2014), *available at* http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf.

[2] FDA, Oversight of Laboratory Developed Tests, Notice of Public Meeting, 75 Fed. Reg. 34463 (June 17, 2010).

[3] Letter from U.S. Senators Edward J. Markey, Richard Blumenthal, Elizabeth Warren and Sherrod Brown to Mr. Brian Deese, Acting Director, OMB (July 2, 2014), *available at* http://www.markey.senate.gov/imo/media/doc/2014-07-02_Deese_LDTs.pdf.

manufacturers and sold to clinical laboratories. Historically, FDA has exercised its enforcement discretion over LDTs, meaning that the agency has generally not enforced the medical device requirements under the FDCA and FDA regulations for LDTs.

Although clinical laboratories that develop and use LDTs have generally not been regulated by FDA under the FDCA, they are subject to oversight and regulation by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).[4] Under CLIA, laboratories that offer LDTs must be certified to perform high-complexity testing, which requires inspection by CMS, establishment of a quality assurance and proficiency testing program, and compliance with other requirements. Laboratories must also validate LDTs to ensure that the results are accurate and reproducible.

In the 1990s, FDA adopted a position that LDTs are medical devices subject to the requirements of the FDCA, but the agency would exercise its enforcement discretion not to require compliance by LDTs. FDA's position on LDTs changed in 2010, when FDA announced its intention to implement a risk-based approach to regulating LDTs.[5] At that time, FDA cited the evolution of LDTs from "relatively simple, well-understood pathology tests or that diagnosed rare diseases and conditions that were intended to be used by physicians and pathologists within a single institution" to complex tests used "to assess high-risk but relatively common diseases" and "to inform critical treatment decisions" that were performed in geographically distant labs instead of within the patient's health care setting.[6] Subsequently, FDA stated that it would issue guidance documents to implement a regulatory system for LDTs.

FDA's authority to regulate LDTs under the FDCA has been the subject of significant debate. Two citizen petitions had been filed arguing that FDA lacked jurisdiction over LDTs: one filed by the Washington Legal Foundation in 2006[7] and one filed by the American Clinical Laboratory Association in 2013.[8] In addition, Genentech, Inc. filed a citizen petition in 2008 requesting that FDA regulate all LDTs, or at least LDTs used in "drug or biologic therapeutic decision making."[9] The same day FDA notified Congress of its intent to issue the draft guidance documents, it denied all three citizen petitions.[10] In addition, several bills have been introduced in Congress in the last several years proposing alternative regulatory systems for LDTs, including a proposal to amend CLIA.

Proposed Framework

FDA states in the LDT Framework Documents that FDA "believes it should no longer generally exercise enforcement discretion towards all LDTs."[11] The framework outlined by FDA includes a risk-

[4] 42 U.S.C. § 263a; Pub. L. No. 100-578, 102 Stat. 2903 (1988).
[5] FDA, Oversight of Laboratory Developed Tests, Notice of Public Meeting, 75 Fed. Reg. 34463 (June 17, 2010).
[6] Id.
[7] Washington Legal Foundation, Citizen Petition, Docket No. FDA-2006-P-0149-0004 (Sept. 28, 2006), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2006-P-0149-0004.
[8] American Clinical Laboratory Association, Citizen Petition, Docket No. FDA-2013-P-0667-0001 (June 4, 2013), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0667-0001.
[9] Genentech, Inc., Citizen Petition, Docket No. FDA-2008-P-0638-001 (Dec. 5, 2008), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2008-P-0638-0001.
[10] Letter from Leslie Kux, Assistant Commissioner for Policy, FDA, to Daniel J. Popeo and Richard A. Samp, Washington Legal Foundation, Docket No. FDA-2006-P-0149-0010 (July 31, 2014), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2006-P-0149-0010; Letter from Leslie Kux, Assistant Commissioner for Policy, FDA, to Alan Mertz, American Clinical Laboratory Association, Docket No. FDA-2013-P-0667-0008 (July 21, 2014), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0667-0008.
[11] LDT Framework for Regulatory Oversight at 10.

based, phased-in approach towards regulating LDTs that would include for certain LDTs, registration and listing or "notification," and compliance with medical device reporting requirements, premarket review requirements, and the Quality System Regulation (QSR).

How are LDTs Defined?

In the LDT Framework Documents, FDA defines an LDT as "an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory."[12]

A diagnostic device that is "designed or manufactured completely, *or partly*, outside of the laboratory that offers and uses it" is not considered an LDT by FDA. [13] The LDT definition therefore does not include (1) devices developed within one laboratory and transferred to another laboratory within a network of laboratories owned by the same entity or (2) a device of which a key component was contract manufactured by a third party.[14]

Although FDA believes that devices that are currently offered by laboratories as LDTs, but which do not meet FDA's definition of LDT are in violation of the FDCA, FDA recognizes that it is important to apply a framework over laboratory tests that "ensures consistency in the testing market" and avoids disruption in access to these tests. Therefore, FDA intends to apply the same enforcement discretion and phased-in approach to any IVD that is offered as an LDT by a CLIA-certified laboratory, even if the test does not technically meet FDA's definition of an LDT.[15]

How Would LDTs be Classified?

FDA would rely upon the existing medical device classification system (Class I - Class III) to evaluate the risk of a category of LDTs and, where appropriate, would use expert advisory panels to help classify devices not previously classified by FDA.[16] To determine the risk of the LDT, FDA intends to consider several factors, such as (1) whether the LDT is intended for use in high risk diseases/conditions or patient populations; (2) whether the LDT is for use in screening or diagnosis; and (3) the nature of the clinical decision that would be made based on the test result and whether other information about the patient would be available to assist in making the clinical decision.[17] In order to provide additional clarity, FDA intends to issue a draft guidance describing what the agency considers generally to be Class, I, II or III within 18 months of finalizing the LDT Framework for Regulatory Oversight document.[18] The draft guidance would be available for comment in advance of an advisory panel meeting on LDT risks and enforcement prioritization. FDA intends to finalize the classification guidance within 24 months of finalizing the guidance on the LDT framework.[19]

What is FDA's Proposed LDT Framework?

Under the approach described in the LDT Framework Documents, FDA would regulate LDTs according to three general categories:

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[12] Id. at 4.
[13] Id. (emphasis added).
[14] Id.
[15] Id. at 5.
[16] Id. at 10.
[17] Id. at 10-11.
[18] Id. at 11.
[19] Id. at 25.

1. **Continued Enforcement Discretion**. For a first group of LDTs, FDA would continue to exercise full enforcement discretion. This means that FDA would not impose medical device regulatory requirements on these types of LDTs:

- *LDTs used solely for forensic (law enforcement) purposes*.
- *LDTs 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 conducting real and "virtual" crossmatch tests.[20]

2. **Partial Enforcement Discretion**. For a second group of LDTs, FDA intends to continue to exercise enforcement discretion with respect to (i) applicable premarket submission requirements, and (ii) QSR requirements. However, such LDTs must comply with (i) either the "notification" procedures described by FDA (discussed in detail below) or the registration/listing requirements of 21 CFR Part 807, and (ii) adverse event reporting requirements of the medical device reporting (MDR) regulation of 21 CFR Part 803. This group of LDTs includes:

- *Low-risk LDTs* (Class I devices).[21]
- *LDTs for rare diseases*. These are LDTs that are "developed to diagnose or to help to diagnose a disease or condition with an incidence of fewer than 4,000 patients per year."[22]
- *"Traditional" LDTs*, which are those LDTs that reflect the type of LDT available in 1976, when FDA started its enforcement discretion policy with LDTs. FDA intends to consider four factors in determining whether an LDT would be considered a "Traditional LDT":
  - 1) whether the test meets the definition of LDT in the guidance;
  - 2) whether the LDT is both manufactured and used by a health care facility laboratory for a patient that is being diagnosed and/or treated at the same health care facility or within that facility's healthcare system;
  - 3) whether the LDT is comprised of only legally marketed components and instruments; and
  - 4) whether the LDT is interpreted by qualified laboratory professionals without use of automated instrumentation or software for interpretation.[23]
- *"LDTs for Unmet Needs*." These are LDTs that are performed when no FDA-approved or cleared equivalent device is available. In determining whether an LDT qualifies as an "LDT for Unmet Needs" FDA proposed to consider three factors:
  - 1) whether the test meets the definition of LDT in the guidance;
  - 2) whether there is no FDA cleared or approved IVD available for that specific intended use; and
  - 3) whether the LDT is both manufactured and used by a health care facility laboratory for a patient that is being diagnosed and/or treated at that same health care facility or within that facility's healthcare system.[24]

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[20] Id. at 15.
[21] Id. at 11.
[22] Id. at 19-20. FDA clarifies that an LDT would not be considered an "LDT Used for Rare Diseases" if the applicable disease or condition has an incidence of fewer than 4,000 patients per year, but there are more than 4,000 patients per year who would be subject to testing with the LDT. Id.
[23] Id. at 20.
[24] Id. at 21.

However, once FDA clears or approves an IVD for the same intended use as the LDT, the LDT would lose its status as an "LDT for Unmet Needs" and FDA intends to enforce the premarket review requirements if the LDT falls within one of FDA's enforcement priorities.[25]

3. **Enforcement of Premarket Submission and Other Regulatory Requirements.** For a third group of LDTs, FDA will require compliance with: (i) FDA's "notification" procedures or registration/listing, (ii) MDR reporting, (iii) QSR requirements, and (iv) premarket clearance or approval. This group of LDTs include tests not falling into one of the previously described categories, including:

- *Moderate risk (Class II) LDTs*.
- *High-risk (Class III) LDTs*. These include:
  - 1) "Highest Risk" LDTs:
    a. LDTs with the same intended use as a cleared or approved companion diagnostic;
    b. LDTs with the same intended use as an FDA-approved Class III medical device; and
    c. certain LDTs for determining the safety or efficacy of blood or blood products.
  - 2) LDTs "of higher concern" to the agency (which would likely receive higher priority in the phased-in enforcement):
    d. LDTs that act like companion diagnostics (i.e. LDTs that claim to enhance the use of a specific therapeutic product but which are not included in the therapeutic product labeling);
    e. screening LDTs for serious diseases and/or conditions intended for use in asymptomatic patients with no other available confirmatory diagnostic product or procedure (e.g. screening device for malignant cancers); and
    f. diagnostic devices for certain infectious diseases with high-risk intended uses.[26]
  - 3) *All other Class III LDTs*.[27]

With respect to QSR requirements, FDA has not provided further guidance on how the QSRs would be applied, or how they would interrelate with existing CLIA requirements that laboratories must follow. FDA intends to continue exercising enforcement discretion for QSR compliance until a manufacturer of a given LDT submits a PMA or FDA issues a 510(k) clearance order for the LDT.

In addition, FDA notes that the agency intends to continue exercising enforcement discretion for low-risk LDTs: (1) LDTs classified as Class I diagnostic devices, including those not exempt from 510(k) submission requirements; and (2) LDTs classified as Class II diagnostic devices that are exempt from 510(k) submission requirements.[28]

LDTs subject to premarket review would be required to submit either a premarket notification (510(k)) submission or a premarket approval application (PMA). The LDT Framework Documents do not provide details on what data would be required to meet premarket review requirements. FDA does note that it may not be necessary for sponsors to conduct extensive new studies to demonstrate clinical validity of analytes or markers that have had their clinical validity already established in the literature. However, the sponsor would need to demonstrate that any changes in

[25] Id. at 22.
[26] Id. at 25-26.
[27] Id. at 11-12.
[28] Id. at 28.

technology or methodology that differ from that used in the literature do not affect the clinical validity of the LDT.[29] The timing for such premarket review requirements is described in the chart below.

What is the Notification Option?

The LDT Framework Documents describe a "notification" option for laboratories. Under that option, laboratories may choose to "notify" FDA that they are offering LDTs and provide the FDA-required information about each LDT, instead of complying with the registration and listing requirements described in 21 CFR Part 807. The notification is to be submitted within six months of the issuance of the final guidance for LDTs then on the market and for LDTs first marketed within that six months. FDA intends to exercise enforcement discretion with respect to registration and listing requirements for laboratories that provide "notification" to FDA.[30]

Laboratories that use the notification requirement would avoid medical device registration fees and the IRS medical device tax requirement, since the IRS defines a taxable medical device as a "device that is listed" with the FDA (see our previous blog on the medical device tax regulation, here).

The notification option would be available only for establishments that perform *only* LDTs. Any establishment that offers other medical devices in addition to LDTs will be subject to the registration and listing requirements.[31] In addition, laboratories developing LDTs that submit a 510(k) or PMA to the FDA would be required to comply with the registration and listing requirements once a premarket submission is submitted for any one LDT. [32]

FDA would use the notification process to collect information on the LDTs being used by laboratories in order to classify LDTs by risk level and assist the agency in determining its priorities for enforcement of the premarket review requirements.[33] Notification information would be submitted online through FDA's website, and would include the following information:

- laboratory name and contact e-mail,
- test name,
- monthly test volume,
- intended use,
- clinical use of the test (e.g. diagnosis, prognosis, monitoring, etc.),
- analytes measured or organisms detected,
- disease or condition for which the device is indicated,
- patient population (and whether it includes pediatric patients),
- sample type,
- test method, and
- whether the test is a modification of an FDA cleared or approved test (and if so, what modifications were made).[34]

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[29] Id. at 12, 27.
[30] Id. at 16.
[31] Id. at 18.
[32] Id. at 17.
[33] LDT Framework for Regulatory Oversight at 16; LDT Notification and Reporting at 5.
[34] LDT Notification and Reporting at 21-23.

FDA intends to make notification information public after redacting information which FDA is prohibited from disclosing.[35]

What is the Proposed Timeframe for Enforcement?[36]

LDT Category	Notification or Registration and Listing	Medical Device Reporting	Premarket Review	Quality System Regulation Requirements
Highest-Risk (Class III)	*Six Months after Finalization of Guidance* - Notification if developing an LDT when guidance is finalized or if offering new LDT within 6 months of finalization. *Prior to Offering for Clinical Use* - Notification if offering new LDT after initial 6 month timeframe. *Upon Submission of PMA* - If a premarket submission is made to FDA, the laboratory needs to register and list.	*Six Months after Finalization of Guidance.*	*12 Months after Finalization of Guidance* - If offering an LDT when guidance is finalized. *Immediately* - If developing a new LDT after finalization of guidance.	*Upon Submission of a PMA* - FDA would exercise enforcement discretion until a manufacturer submits a PMA. Clinical labs using the LDT would be required to have quality system in place at the time of PMA submission.
High-Risk (Class III)	*Six Months after Finalization of Guidance* - Notification if developing an LDT when guidance is finalized or if offering new LDT within 6 months of finalization. *Prior to Offering*	*Six Months after Finalization of Guidance.*	*36 Months after Finalization of Guidance for "Highest Priority"* - Issuance of FDA priority list within 24 months after finalization of guidance and enforcement of premarket review 12 months after	*Upon Submission of a PMA* - FDA would exercise enforcement discretion until a manufacturer submits a PMA. Clinical labs using the LDT would be required to have quality system in place at the time

[35] LDT Framework for Regulatory Oversight at 16.
[36] FDA provides a chart with similar information in Appendix A of the LDT Framework for Regulatory Oversight.

	for Clinical Use - Notification if offering new LDT after initial 6 month timeframe. *Upon Submission of PMA* - If a premarket submission is made to FDA, the laboratory needs to register and list.		priority list announced. *36 Months to 5 Years* - FDA intends to complete phased-in enforcement of premarket review for remaining Class III LDTs within a 5 year period of finalization of guidance.	of PMA submission.
Moderate-Risk (Class II)	*Six Months after Finalization of Guidance* - Notification if offering an LDT when guidance is finalized or if offering new LDT within 6 months of finalization. *Prior to Offering for Clinical Use* - Notification if offering new LDT after initial 6 month timeframe. *Upon Submission of 510(k)* - If a premarket submission is made to FDA, the laboratory needs to register and list.	*Six Months after Finalization of Guidance.*	*5 years to 9 years* - FDA intends to phase-in enforcement after completion of phase-in of Class III devices. Issuance of FDA priority list within 4 years after finalization of guidance and complete phase-in enforcement within 9 years of finalization of guidance.	*Upon Issuance of 510(k) Clearance Order* - FDA would exercise enforcement discretion until FDA issues a 510(k) clearance. Clinical labs using the LDT would be required to have quality system in place prior to market launch for 510(k) LDTs.
Low-Risk (Class I) **LDTs for Rare Diseases** **Traditional LDTs** **LDTs for Unmet**	*Six Months after Finalization of Guidance* - Notification if developing an LDT when guidance is finalized or if	*Six Months after Finalization of Guidance.*	*Enforcement Discretion.**	*Enforcement Discretion.*

Needs	offering new LDT within 6 months of finalization. *Prior to Offering for Clinical Use* - Notification if offering new LDT after initial 6 month timeframe.			
Solely used for forensic (law enforcement) purposes **Used in CLIA-certified, high-complexity histocompatibility laboratories for transplantation**	*Enforcement Discretion.*	*Enforcement Discretion.*	*Enforcement Discretion.*	*Enforcement Discretion.*

*See discussion above regarding "LDT for Unmet Needs" - Once FDA clears or approves an IVD for the same intended use as the LDT, the LDT will no longer be in this category.

Conclusion

The LDT Framework Documents describe FDA's proposed framework for regulating LDTs under the FDCA. However, there remains uncertainty as to what the final framework of regulation of LDTs will look like and when that framework would be imposed, as the draft guidance documents will be open for public comment once published and there is no set timeframe for finalization of the draft guidance documents. Given the ongoing debate over whether FDA has the statutory authority to regulate LDTs, and the significant impact the proposed framework would have on the development and use of LDTs, the draft guidance documents are expected to be highly contentious.

In addition, the LDT Framework Documents do not provide details on how FDA intends to handle the large resource burden of enforcing these requirements for the estimated over ten thousand LDTs currently offered by several thousand laboratories. FDA intends to review PMAs for high-risk LDTs, but for most moderate-risk LDTs, the agency would utilize FDA-accredited third-party review of premarket submissions.[37] FDA has not yet specified the risk classification of existing LDTs and the classification process is expected to take several years. Likewise, FDA's plan to enforce the QSR requirements remains unclear, although FDA would expand its third party inspection program for surveillance inspections and "explore opportunities to coordinate with and leverage existing programs."[38]

The LDT Framework Documents leave open many questions with which laboratories and FDA will have to grapple, for example:

[37] Id. at 12, 27.
[38] Id. at 28.

- How will FDA apply general risk classifications to LDTs and reduce uncertainty for labs and providers until risk classes are established?
- How would FDA regulation be reconciled with regulation under CLIA? For example, will laboratories be required to comply with the complete QSR and thus be subject to duplicative and perhaps conflicting regulation, or will FDA consider some or all CLIA requirements as satisfying QSR?
- Where is the line between FDA device regulation and the practice of laboratory medicine?
- Will FDA have the resources to handle potentially thousands of premarket submissions for LDTs?
- How would laboratories obtain clarity as to whether a particular LDT is subject to enforcement discretion as a "Traditional LDT" or "LDT for Unmet Needs" under the factors described in the guidance?
- How would FDA apply its usual safety and effectiveness approach of evaluating one analyte and one disease or condition in the context of LDTs that often involve multiple analytes?
- When would an iterative improvement to an LDT be significant enough to require a new notification?
- What is the impact on instrument and reagent manufacturers whose instruments and reagents are used by laboratories offering LDTs?

If FDA proceeds to publish draft guidance documents, as stated in its notification to Congress, they will be published to a docket on regulations.gov sometime after September 29, 2014. FDA's website indicates that there will be a 90-day comment period on the draft guidance.[39]

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[39] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm.