



Regulatory Overview of Proposed LDT Framework

By Benjamin D. Berg & Meaghan Bailey, RAC

On July 31, 2014, the U.S. Food and Drug Administration (FDA or the Agency) notified both the Senate Committee on Health, Education, Labor and Pensions and the House Committee on Energy and Commerce of the Agency's intent to issue two draft guidance documents on FDA's regulation of laboratory developed tests: "Framework for Regulatory Oversight of Laboratory Developed Tests" and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests." These two draft guidances were published on October 3, 2014. These draft guidance documents indicate a significant shift in FDA regulatory policy toward laboratory developed tests (LDTs). FDA has

previously exercised enforcement discretion over all LDTs, and based on the changing nature of LDTs from simple pathology to complex genetic testing, FDA has now taken the first actionable step toward enforcing the requirements of the Federal Food, Drug, and Cosmetic Act (the Act) on LDTs, using a risk-based approach.

Background

LDTs, like in vitro diagnostics (IVDs), are regulated by FDA as a type of medical device used in humans. However, the Agency has practiced a policy of enforcement discretion over LDTs,¹ by not subjecting them to the requirements of the



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Act.² Instead, LDTs and the laboratories that develop them have been regulated since 1967 by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). CLIA certifications are awarded at the state level and while the level of oversight can vary state by state, CLIA requirements generally address the analytical validation of a laboratory test specific to a laboratory.

FDA Concerns

When the Medical Device Amendments of 1976 were passed, the majority of LDTs, “Traditional LDTs,” were manual procedures developed by local laboratories intended to be used for rare diseases and for the local population. Further, these tests were similar to well-characterized standard diagnostic devices, were manufactured with components legally marketed for clinical use, and were used and interpreted by healthcare practitioners within a single institution. However, over time the use, manufacture and complexity of LDTs have greatly evolved. “Modern LDTs” are used in laboratories that are independent of the healthcare delivery entity, and rely more heavily on high-tech instrumentation and software for results and interpretation.³ Further, the Agency has found that Modern LDTs are frequently being used for high-risk diseases across many populations. FDA recognized that some Modern LDTs, such as cancer diagnostics, were intended for the same use as other IVDs, which underwent clearance or approval. CLIA requirements are intended to confirm the analytical reliability of a test, rather than safety and effectiveness of clinical performance, and so in 2013, Dr. Margaret Hamburg first stated that the

Agency was working to assure that the accuracy and clinical validity of high-risk tests are established before they come to market.

FDA Proposed Regulatory Approach

In its October 3 draft guidance, FDA proposes a risk-based approach to regulating LDTs, which follows the three-class system currently used to regulate medical devices. In determining LDT risk classification, FDA provides the following considerations:

- Whether the LDT is intended for use in high-risk disease/conditions or patient populations
- Whether the LDT is used for screening or diagnosis
- The nature of the clinical decision that will be made based on the test result
- What other information is available to the physician/pathologist to assist in the clinical decision
- What other alternative diagnostic and treatment options are available
- Potential consequences of erroneous results
- Number and type of adverse events

It is the risk profile of the LDT that will determine the level of regulatory oversight. In its notification of intent to regulate LDTs to Congress, FDA also described how, within 24 months of its issuance of the final guidance on the regulatory oversight framework for LDTs, the Agency plans to issue a second, related guidance document entitled, “Classification of LDTs.” This guidance will provide examples of LDTs that fit each risk classification.

The three categories outlined in the proposed LDT regulatory framework guidance are described in detail

below, along with the associated regulatory requirements.

LDTs With Full Enforcement Discretion

FDA plans to continue full enforcement discretion for two types of LDTs: LDTs used solely for forensic (law enforcement) purposes and LDTs used in CLIA-certified high-complexity histocompatibility laboratories for transplantation. The Agency believes that protections set forth in the judicial process are sufficient to ensure sample integrity and test accuracy for forensic LDTs. For LDTs used in CLIA-certified high-complexity histocompatibility laboratories for transplantation, FDA is concerned that enforcement of the regulatory requirements could lead to a shortage of these tests. These LDT types are exempt from all of the requirements in the Act including notification to FDA, registration and listing, premarket review, adverse event reporting and quality system requirements.

LDTs With Partial Enforcement Discretion

FDA identifies four types of LDTs that will only have to comply with some of the requirements of the Act: 1) Low-risk LDTs (Class I devices), 2) LDTs used for rare diseases, 3) Traditional LDTs and 4) LDTs for unmet needs when no FDA cleared or approved alternative exists. For each of these LDT types, FDA only plans to enforce notification and/or registration and listing, and MDR requirements. FDA believes that these LDTs have sufficient other controls, such as meeting the definition of a Traditional LDT, to establish the safety and effectiveness of the LDT, and does not want to create an overly burdensome environment that would

prevent LDTs for unmet needs from coming to market.

Notification and/or Registration and Listing Requirements:

- The notification requirement is a new process proposed by FDA to allow laboratories to bypass the registration and listing requirements. As part of this process, laboratories that market or plan to market LDTs can notify FDA of the basic information regarding the LDT prior to marketing. The Agency will not enforce registration and listing requirements for laboratories that notify FDA, as long as they continue to make notifications to the Agency about new tests.
- Medical Device Reporting (MDR) Requirements.
- FDA plans to enforce all the requirements of 21 CFR 803, including adverse event reporting, six months after finalization of the guidance document.

LDTs Subject to Full Requirements of the Act

Moderate and high-risk LDTs will be subject to all of the requirements of the Act, and will be classified as Class II (moderate-risk) and Class III (high-risk) devices, respectively. In addition to MDR and registration and listing requirements, these LDTs will have to further comply with premarket review (510(k)s and/or PMAs) and quality system requirements. FDA believes that the risk profiles for these LDTs require these additional controls in order to ensure safety and effectiveness.

For all new highest-risk LDTs, FDA plans to immediately begin enforcing premarket review requirements upon finalization of the guidance document. For Class II and III LDTs that are

currently on the market, FDA intends to continue to exercise enforcement discretion of premarket review requirements for a period of time after finalization of the guidance document, with the timing of a premarket submission dependent upon the risk prioritization of the LDT.

Phased Approach

Except for new LDTs as described above, FDA does not intend to begin enforcing these requirements as soon as the guidance is finalized, but rather is taking a phased approach. In doing so, the Agency is hoping to increase transparency with industry to allow laboratories time to prepare for enforcement. Initially, FDA plans to focus its enforcement attention on the high-risk LDTs. FDA has defined these devices as LDTs with the same intended use as approved companion diagnostics, LDTs with the same intended use as approved Class III medical devices, and certain LDTs for determining safety and effectiveness of blood or blood products. Laboratories with these types of LDTs will have 12 months to submit a premarket approval application. FDA expects to publish a list of remaining high-risk LDTs in year 2 after the guidance is finalized, and in year 4 for moderate-risk LDTs, as based on input from Advisory Committee Panels and the public. Premarket submissions or applications would be expected for the remaining high-risk LDTs between years 3 and 5.

Between years 5 and 9 after the final guidance, FDA will gradually begin to enforce the regulations for moderate-risk LDTs. **Appendix A** provides a table detailing the regulatory requirements of each product type and when the enforcement of those requirements will take effect.

To accommodate for the influx of premarket reviews, and to help facilitate an efficient review process for LDTs, FDA plans to further use the third-party review program. Additionally, the Agency intends to expand its third-party inspection program for surveillance inspections.

Industry Commentary and FDA Next Steps

The proposed FDA regulation of LDTs has been highly contested across the clinical laboratory and diagnostic device industries.

Prior to FDA's notification, the American Clinical Laboratory Association (ACLA) submitted a citizen's petition to FDA asking the Agency to not issue guidance or a proposed or final rule intending to regulate LDTs as devices, and to confirm that LDTs are not medical devices under the Act. Additionally, a group of hospitals, academic health centers and clinical laboratories wrote a letter to the Obama administration urging the White House to not allow FDA to regulate LDTs. In this letter, and in commentary since publication of FDA's notification, members of the clinical laboratory industry have argued that the current regulatory framework provides sufficient oversight for these tests, and that FDA regulation would stifle innovation that they find critical to the growth of personalized medicine and emerging public health concerns. Further, many members of this industry believe that LDT services fall under practice of medicine and thereby FDA does not have authority to regulate LDTs, and they are concerned that FDA has neither the funds nor the resources to appropriately enforce this regulation.

Members of the diagnostic device industry, however, have praised FDA for its intent to regulate LDTs. This industry, as often advocated for by AdvaMedDx, has commented that LDTs are being more commonly used to diagnose and guide the treatment for high-risk diseases and have the same intended uses as diagnostic devices that are currently under FDA enforcement. Such groups feel that this regulation “evens the playing field.” Additionally, patient advocacy groups and some physician groups have stressed

concerns about the safety of LDTs.

The U.S. House Energy and Commerce Health Subcommittee held a hearing on September 9, 2014 to question and gain further insight from FDA and industry groups to the extent and impact of this regulation. Similar to the comments and concerns expressed publicly by various stakeholders before the notification of intent was published, the subcommittee hearing also reflected lawmakers’ concerns that FDA is overregulating or is too under-resourced to be able to effectively

regulate LDTs. Other stakeholders presenting during the meeting had praise for the proposed regulations.

FDA Timing

Starting on October 3, 2014, FDA opened a 120-day public comment window for the regulatory framework draft guidance. FDA has since been engaging with stakeholders through webinars and a meeting with the Clinical Laboratory Improvement Advisory Committee (CLIAC). The Agency held a public meeting on January 8-9, 2015 with industry stakeholders to

APPENDIX A

LDT Category	Notification/Registration and Listing	MDR Requirements	Premarket Review	Quality Systems
LDTs for forensic use	Not enforced	Not enforced	Not enforced	Not enforced
LDTs used in CLIA-certified high-complexity histocompatibility laboratories for transplantation	Not enforced	Not enforced	Not enforced	Not enforced
Low-risk LDTs	Notification within six months of guidance finalization. If no notification, registration and listing are required.	Will be enforced upon guidance finalization.	Not enforced	Not enforced
LDTs used for rare diseases	Notification within six months of guidance finalization. If no notification, registration and listing are required.	Will be enforced upon guidance finalization.	Not enforced	Not enforced
LDTs for unmet needs	Notification within six months of guidance finalization. If no notification, registration and listing are required.	Will be enforced upon guidance finalization.	Not enforced	Not enforced
Traditional LDTs (LDTs that are similar to those available in 1976, when FDA began its policy of enforcement discretion)	Notification within six months of guidance finalization. If no notification, registration and listing are required.	Will be enforced upon guidance finalization.	Not enforced	Not enforced
Moderate-risk LDTs (Class II medical devices)	Notification within six months of guidance finalization. If no notification, registration and listing are required.	Will be enforced starting six months following guidance finalization.	Premarket review will be required 5-9 years after guidance finalization.	Enforced upon 510(k) clearance.
High-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)	Notification within six months of guidance finalization. If no notification, registration and listing are required.	Will be enforced upon guidance finalization.	LDTs already marketed will have 12 months to comply with premarket review requirements. New LDTs will have to comply as soon as the guidance is finalized.	Enforced upon guidance finalization.

discuss the scope and intent of FDA regulation over LDTs. Although FDA representatives have not made specific comments about the timing of a final guidance, or possibility of issuing a second draft guidance, the recently published CDRH Fiscal Year 2015 Proposed Guidance Prioritization⁴ lists the LDT draft guidance under priority A for final guidance in 2015. The Agency does expect it will take up to nine years after the final guidance

is published for the submission, review and approval or clearance of FDA applications for high to moderate risk LDTs to take place. ▲

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1. As defined in the anticipated draft guidance document, “Framework for Oversight of Laboratory Developed Tests,” LDTs are defined as an IVD that is intended for clinical use and designed, manufactured, and used within a single laboratory.
 2. FDA generally does not exercise enforcement discretion for

direct-to-consumer (DTC) tests regardless of whether they meet the definition of an LDT.

3. Anticipated Details of the Draft Guidance for Industry, FDA Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs). US FDA Website. <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf> July 31, 2014.
4. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MDUFAIII/ucm321367.htm#complete>.