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FDA Takes Another Step Toward Regulating LDTs

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On Oct. 1, 2014, the U.S. Food and Drug Administration took the next step toward regulating laboratory developed tests by publishing its new plan to regulate LDTs in the form of two draft guidance documents: "Framework for Regulatory Oversight of Laboratory Developed Tests" (the Framework Guidance) and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests" (the Notification Guidance).[1]

The two guidance documents were formally published in the Federal Register on Oct. 3 (and were prepublished by the FDA in letters to the House and Senate on July 31), as required by Section 1143 of the Food and Drug Administration Safety and Innovation Act.

The FDA's intent to regulate LDTs is contentious. In a congressional hearing on Sept. 9, Jeffrey E. Shuren, director of the FDA's Center for Devices and Radiological Health, was questioned at length regarding the FDA's proposed oversight of LDTs. The questions were informative as they raise important issues which include, among other things:

- is the FDA conforming with the Administrative Procedure Act by using guidance documents instead of notice and comment rulemaking?;
- if the FDA has the statutory authority to regulate LDTs;
- what is the FDA's basis for believing that it is now necessary to regulate LDTs and that there are flawed LTDs on the market?;
- what are the additional burdens that will be imposed on the FDA and LDT providers because of the proposed regulations?;
- will the proposed regulations stifle innovation?;
- the source of FDA resources for the increased regulation; and
- duplication between FDA regulation and CLIA.

After the guidance documents formally publish in the Federal Register, an expanded 120-day comment period will take effect.

The Framework Guidance provides the FDA's plan to phase in and prioritize, based on risk, the regulation of LDTs. The Notification Guidance explains how clinical laboratories will notify the FDA of LDTs they manufacture and describes the Medical Device Reporting requirements for LDTs. The FDA's regulation of LDTs, when finalized and completely implemented, will significantly affect companies that develop and market LDTs.

The Framework Guidance

It is estimated there are currently 11,000 LDTs offered by 2,000 laboratories in the U.S.[2] The FDA defines a LDT "as an [in vitro diagnostic device] that is intended for clinical use and designed, manufactured and used within a single laboratory."[3][4] LDTs are also known as "in-house developed" tests or "home brew" tests.[5] Although the FDA asserts it always had the legal authority to regulate LDTs since 1976 as medical devices,[6] the agency initially exercised its discretion to generally not regulate LDTs. This was because most LDTs were putatively provided by local community laboratories, met the needs of a local patient population, were similar to well-characterized, standard diagnostic devices, and were typically used and interpreted directly by physicians and pathologists who were treating patients in the facility performing the tests.[7]

The FDA asserts that times have changed. Specifically, the FDA asserts that LDTs are now often independent of the health care delivery entity, are frequently manufactured with components and instruments that are not legally marketed for clinical use, and rely on high-technology instrumentation and software to generate results and clinical interpretations.[8] The FDA also believes that LDTs are increasingly critical for clinical management decisions for high-risk diseases and personalized medicine.[9] The FDA "identified problems with several high-risk LDTs including: claims that are not adequately supported with evidence; lack of appropriate controls yielding erroneous results and falsification of data."[10] Accordingly, the FDA has now decided to exercise its statutory authority to regulate LDTs. The FDA's decision will directly and significantly impact the estimated 2,000 laboratories offering approximately 11,000 LDTs, as well as a very large number of tests in development.

Since 1988, LDTs have been regulated under the CLIA.[11] CLIA regulates LDTs to ensure reliable test results (i.e., CLIA focuses on the quality of laboratory procedures and personnel and ensures that the LDT accurately detects the presence or absence of target analyte(s) in a patient specimen, also known as analytical validity). The FDA's proposed regulation, while somewhat overlapping in scope, is different in that it would:

- regulate the safety and efficacy of the test, require reporting of adverse events for certain LDTs, and

- require proof of clinical validity for certain LDTs (i.e., that the presence or absence of target analyte(s) is associated with a clinical outcome such as the presence or absence of a disease or that a patient with a specific genetic mutation would do better with a specific drug), and

- for higher-risk LDTs, the FDA's proposed regulation would also require premarket approval or clearance under the premarket notification procedure, or 501(K) premarket notification.[12]

The FDA intends to take a risk-based approach to regulation and prioritization of LDTs. The FDA notes that medical devices are "classified as Class I, II or III based upon the controls necessary to provide a reasonable assurance of the safety and effectiveness of the device[s]."[13] Class I devices are "subject

only to general controls and generally represent the lowest-risk category of devices" while "Class III devices ... generally represent the highest-risk devices."[14] The FDA will rely on the existing medical device classification system to evaluate the risk of a category of LDTs.[15] LDTs will be classified as low risk (Class I devices), moderate risk (Class II devices) and high risk (Class III devices).

Corresponding to the classes of LDTs, there will be three regulatory levels of LDTs: (1) LDTs subject to full enforcement discretion (minimal regulation), (2) LDTs subject to partial enforcement discretion (moderate regulation) and (3) LDTs subject to full FDA regulation. For companies that offer or plan to offer LDTs, the LDT classification is important because it determines the level of review by the FDA, with longer review times and more stringent review criteria translating into more time and expense to bring the LDT to market. LDTs will thus be regulated as outlined below.

Minimal or No Regulation

The FDA will exercise enforcement discretion for:

- LDTs used solely for forensic (i.e., law enforcement) purposes; and
- LDTs for transplantation when used in a CLIA-certified, high-complexity histocompatibility laboratory.[16]

Moderate Regulation

The FDA intends to exercise enforcement discretion for applicable premarket review requirements and quality systems requirements, but enforce other applicable regulatory requirements including registration, listing and adverse event reporting for:

- low-risk LDTs (Class I devices);
- LDTs for rare diseases[17] ;
- traditional LDTs[18][19]; and
- LDTs for unmet needs[20] when no FDA-approved or cleared equivalent device is available.[21]

Full FDA Regulation

For what the FDA considers to be so-called high-risk and moderate-risk LDTs, the agency intends to enforce applicable regulatory requirements, including registration and listing (with the option to instead provide notification), adverse event reporting, premarket review and quality system requirements. High-risk LDTs include:

- 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 device; and
- certain LDTs for determining safety and effectiveness of blood or blood products.[22]

For reference purposes, an example of a companion diagnostic test that would likely be categorized as a Class III comes from the current therascreen KRAS RGQ PCR Kit. As characterized by the FDA, the therascreen KRAS RGQ PCR Kit is a real-time qualitative PCR assay used on the Rotor-Gene Q MDx instrument for the detection of seven somatic mutations in the human KRAS oncogene, using DNA

extracted from formalin-fixed paraffin-embedded, colorectal cancer tissue. The therascreen KRAS RGQ PCR Kit is intended to aid in the identification of colorectal cancer patients for treatment with ERBITUX (cetuximab) and VECTIBIX (panitumumab), based on a KRAS no-mutation-detected test result.[23]

According to the draft rules, six months after guidance finalization, LDT manufacturers will be required to notify the FDA if they are manufacturing LDTs and must begin to report significant adverse events to the FDA.[24] Also, the FDA intends to phase in enforcement of premarket review requirements for relevant LDTs over an extended period of time, with "highest-risk" LDT enforcement beginning 12 months after guidance finalization.[25] Laboratories will be required to comply with appropriate quality controls in the FDA Quality System Regulation at the time their PMAs are submitted or the FDA issues a 510(k) clearance order.[26][27][28] Finally, the FDA stated that where an "LDT's analytes/markers that are measured/assessed have had their clinical validity already established in the literature, the FDA believes it may not be necessary for sponsors to conduct extensive new studies to demonstrate clinical validity of the analytes/markers, but the sponsor will need to demonstrate that any changes in technology or methodology that differ from that used in the literature to assess the analyte/marker do not affect the clinical validity of the LDT."[29] However, the degree to which literature can be used in a premarket submission will need further clarification.

The Notification Guidance

The Notification Guidance explains how clinical laboratories will notify the FDA of LDTs they manufacture and describes the MDR requirements for LDTs.[30] Notification requirements include the laboratory name and contact email address; the test name, monthly volume, intended use, and clinical use; the analyte(s) measured; disease for which the diagnostic test is indicated; the patient population for which the test is indicated to be used; whether the patient population includes pediatric patients; the sample type; and the test method. Also required is information on whether the test is a modification of an FDA-approved test, and if so, the modifications that were made.[31]

After a laboratory notifies the FDA, the agency will issue a notification conformation number, which the laboratory will use when filing MDRs. Finally, the Notification Guidance indicates that laboratories will be required to report to the FDA any corrections and removals that were taken to reduce a risk to health posed by the device or to remedy a device problem which may present a risk to health.

Conclusion

The FDA now intends to comprehensively regulate LDTs in a risk-based fashion, which will present significant challenges and opportunities for the estimated 2,000 laboratories offering approximately 11,000 LDTs, as well as potentially thousands in development. In the near term, laboratories that have LDTs on the market or are developing LDTs should: (1) submit comments to the FDA on the draft guidance documents within the expanded comment period after the documents are published in the Federal Register, (2) participate in all open forums that address the soundness and implementation of the new regulatory paradigm and (3) prepare now to meet the anticipated FDA requirements for the tests they are currently manufacturing or will be developing.

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[1] The guidance documents are available here: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf and http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416684.pdf .

[2] A. Pollack, "FDA Acts on Lab Tests Developed In-House," The New York Times, July 31, 2014, available online at: http://www.nytimes.com/2014/08/01/business/fda-to-regulate-lab-developed-test-kits.html?_r=0.

[3] The Framework Guidance at page 5.

[4] The FDA does not consider devices to be LDTs if they are designed or manufactured completely, or partially, outside of the laboratory that offers or uses them. Examples of devices that the FDA does not consider to meet the definition of an LDT are: (1) an entity that owns several clinical laboratories develops a device in one of its clinical laboratories and then transfers the device to several clinical laboratories within its network; and (2) an academic institution develops a device, which it then licenses to or signs an exclusivity agreement with a private corporation that owns a CLIA-certified laboratory. The private corporations CLIA-certified laboratory then begins manufacturing and using the device to provide clinical diagnostic results. For these and other examples, see the Framework Guidance at page 5.

[5] "CLIA Overview ... What Is CMS' Authority Regarding Laboratory Developed Tests (LDTs) and How Does It Differ
from FDA's Authority?" Oct. 22, 2013, available online at https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf.

[6] The asserted legal authority is based on the MDA of the Federal Food, Drug, and Cosmetic Act, which were enacted by Congress in 1976.

[7] The Framework Guidance at page 7.

[8] Id. at pages 7-8.

[9] Id. at page 9.

[10] "Laboratory Developed Tests," FDA, July 31, 2014, available online at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm.

[11] LDTs have been regulated by the Centers for Medicare and Medicaid Services under the CLIA (42 U.S.C. § 263a). The FDA discusses the difference between its proposed oversight and CLIA oversight at pages 9-10 of the Framework Guidance.

[12] The Framework Guidance at, e.g., page 11.

[13] The Framework Guidance at page 11.

[14] The Framework Guidance at page 11.

[15] Id.

[16] The Framework Guidance at page 12.

[17] An LDT for a rare disease will follow the definition of a Humanitarian Use Device in 21 C.F.R. § 814, Subpart H. In practice, this exception is not truly for a rare disease but rather for not-often-performed tests (fewer than 4,000 patients per year tested in the U.S). For example, if an LDT is indicated for a rare disease, but a large subpopulation (e.g., more than 4,000 patients per year) is administered the LDT, then even though the LDT is indicated for a rare disease, the LDT would not qualify as a Humanitarian Use Device (see 21 CFR. § 814.102(a)(5)) and therefore would not be rare disease LDT. See the Framework Guidance at page 20.

[18] Traditional LDTs are "those IVD devices that reflect the types of LDT available when the FDA began its policy of generally exercising enforcement discretion over LDTs in 1976." The Framework Guidance at page 21.

[19] Factors that the FDA will use in determining if an LDT qualifies as a traditional LDT include: whether the device meets the definition of an LDT in the Framework Guidance; whether the LDT is both manufactured and used by a healthcare facility laboratory (such as a hospital or clinic) for a patient that is being diagnosed and/or treated at that same healthcare facility or within the facility's healthcare system; whether the LDT is comprised of only legally marketed components and instruments, general purpose reagents, and various classified instruments; and whether the LDT is interpreted by qualified laboratory professionals, without the use of automated instrumentation or software for interpretation. See the Framework Guidance at page 20.

[20] LDTs for unmet needs are those for which there is no FDA-approved or FDA-cleared equivalent device available. Factors to be considered for determining if an LDT is an LDT for unmet needs include: whether the device meets the definition of an LDT in the Framework Guidance; whether there is no FDA cleared or approved IVD available for the specific intended use; and whether the LDT is both manufactured and used by a health care facility laboratory (such as a hospital or clinic) for a patient that is being diagnosed and/or treated at that same healthcare facility or within the facility's health care system. See the Framework Guidance at page 21.

[21] The Framework Guidance at page 12.

[22] The Framework Guidance at pages 23-24.

[23] Companion diagnostic devices are "in vitro diagnostic devices . . . that provide information that is essential for the safe and effective use of a corresponding therapeutic product." The Framework Guidance at page 24, fn 34.

[24] The Framework Guidance at page 14.

[25] Id.

[26] Id.

[27] Most medical devices are approved through the 510(k) pathway. The remaining medical devices (Class III) utilize PMA. PMA is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. PMA requirements apply to Class III devices, the most stringent regulatory category for medical devices. See "Premarket Approval (PMA)", FDA, July 16, 2014, available online at: http://www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.Htm. The FDA generally proposes to subject high-risk (Class III devices) LDTs to PMA application approval (reviewed by the FDA) and moderate-risk LDTs (Class II devices) to premarket notification (510(k)) submission to be reviewed not by the FDA, but by accredited third parties. Class I LDTs are expected to receive FDA enforcement discretion with respect to applicable premarket review requirements and quality system requirements. See the Framework Guidance at page 13.

[28] The Framework Guidance indicates that high-risk LDTs already on the market would remain on the market during FDA review. See the Framework Guidance at page 13.

[29] The Framework Guidance at page 13.

[30] The Notification Guidance at page 4.

[31] The Notification Guidance at pages 21-23.