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LIFE SCIENCES

SPARKING DISCUSSION AND ADDING FUEL TO THE FIRE: FDA DISCUSSION PAPER ON LABORATORY DEVELOPED TESTS (LDTs)

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On January 13, 2017, the U.S. Food and Drug Administration (FDA) released a discussion paper on laboratory developed tests (LDTs)[1] that outlines a substantial lessening of the level of regulation proposed in a pair of 2014 draft guidances[2] that, in late November, FDA announced it would not be finalizing. While in no way a formal agency position or proposal, the discussion paper is intended by FDA to memorialize its work on the topic to date and to spark public dialogue "on future LDT oversight." The agency also portrays the discussion paper as an attempt to synthesize a broad range of stakeholder feedback and to balance patient protection with continued access and innovation.

Although lauded by some in the laboratory business, the discussion paper has raised concern among patients, scientists, advocates, caregivers, health care professionals, and other stakeholders who have argued for strengthened FDA oversight in light of the increasing complexity of molecular tests. On January 24, 2017, less than two weeks after the publication of the discussion paper, over 30 disease advocacy groups, including the American Cancer Society and the American Heart Association, wrote a letter urging Congress to work with FDA to craft a regulatory framework for LDTs as a priority early in the 115th Congress.[3] Among other things, the letter calls for premarket review, emphasizing that FDA's lack of oversight has become outdated as the complexity of LDTs has grown.

Focused Oversight: Premarket Review

Under FDA's proposed framework, most LDTs that are already on the market would be "grandfathered" and need not comply with most or all FDA regulatory requirements, including premarket review, quality systems, and registration and listing. In addition, six categories of new and significantly modified LDTs could take advantage of the same loose regulatory scheme, including LDTs for rare diseases; certain LDTs for allele typing, antibody screening, and organ and tissue cross-matching; and LDTs whose output is the result of manual interpretation by a qualified professional.

FDA would reserve its right to enforce premarket review, quality systems, and other applicable requirements for any LDT, including the above categories, if the agency determines that:

> (1) the LDT is not, or lacks data to show that it is, analytically and clinically valid;
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> (2) the LDT manufacturer has engaged in deceptive promotion; or
>
> (3) there is a reasonable probability that the LDT will cause death or serious adverse health consequences.

Risk-Based Phased-In Oversight

FDA proposes that premarket review of new and significantly modified LDTs be phased in over four years, rather than the nine years proposed in FDA's 2014 draft guidance. LDTs also would be given two additional years to comply with FDA Quality Systems (Good Manufacturing Practices, or GMP) requirements. However, most LDTs would have to begin reporting serious adverse events and malfunctions in the first year of regulation.

Evidence Standards

FDA's premarket review would complement, not duplicate, CMS's postmarket oversight of laboratory operational processes and its evidence requirements for clinical utility. For analytical validity, FDA anticipates that labs already conducting appropriate evaluations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) to establish performance characteristics would not have to collect additional data to demonstrate such validity for FDA clearance or approval. Further, FDA proposes a reduction of the burden of premarket review where there are third-party proficiency testing programs, certification programs, or accepted reference standards for a specific test. As for clinical validity, FDA anticipates that labs may be able to establish such validity using appropriate sources such as literature or well-curated databases. FDA also notes that labs would be able to leverage prior evidence once an LDT's clinical validity has been established where factors such as indications for use, technology, and standardization are the same. These measures are aimed at lessening the burden on labs and expediting the timeline for premarket review.

Leveraging CMS/CLIA: Quality System Requirements for LDTs

Asserting that existing CMS regulation under CLIA does not meet all of FDA's Quality System Regulation (QSR) requirements, FDA nevertheless proposes to accept certification to CLIA requirements to satisfy most QSR requirements. The exceptions will be for design controls, acceptance activities, and corrective and preventive actions (CAPA). FDA would expand its third-party inspection program for LDTs so that many postmarket inspections could be conducted by FDA-accredited third parties, including accredited organizations and state Departments of Health. Initial inspections would be educational in nature.

Third-Party Review

FDA would expand its third-party premarket review program to include eligible LDTs. For example, FDA is exploring accepting New York State Department of Health (NYSDOH) review in lieu of its own, although CLIA requirements would remain in place.

Transparency

FDA proposes that evidence of the analytical and clinical validity of all LDTs be made publicly available, such as through publication in a journal or on the laboratory's website. FDA would publish its review memorandum for those LDTs that it approves.

Modifications

FDA proposes that labs submit prospective change protocols in their premarket submissions that outline specific types of anticipated changes along with the procedures and criteria used to implement them. Premarket review would be limited to modifications that significantly change performance specifications or intended use of the test and are not made in accordance with the test's approved change protocols.

Conclusion

Despite the expenditure of a tremendous amount of time and effort by many different stakeholders, the future of LDT regulation by FDA is entirely unclear. While the agency notes that it reserves the power to take enforcement action against tests that it considers invalid, the discussion paper gives no hint of what FDA's next step will be, or even whether there will be a next step. Nevertheless, CLIA requirements remain in place, and developing and commercializing LDTs continues to pose certain legal risks. It is important to consult with counsel for assistance in minimizing all risks in this ever-evolving field.

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[1] FDA, Discussion Paper on Laboratory Developed Tests (LDTs) January 13, 2017, available at http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/UCM536965.pdf.

[2] FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories:

"Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" October 3, 2014, available at http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm416685.pdf; FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)" October 3, 2014, available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416684.pdf.

[3] Inside Health Policy, Disease Advocates To Congress: Work With FDA On LDT Oversight Plan, January 27, 2017, available at https://www.focr.org/news/inside-health-policy-disease-advocates-congress-work-fda-ldt-oversight-plan.