

FDA Oversight of Laboratory-Developed Tests Continues To Evolve

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On August 19, 2020, the Trump administration made a major announcement that marks the latest development in the ever-evolving saga of the Food and Drug Administration's (FDA) oversight of laboratory-developed tests (LDTs). The administration declared that LDTs, which are a subset of in vitro diagnostic tests (IVDs) developed and used in-house by clinical laboratories, would not be subject to premarket review by the FDA absent formal agency rulemaking. This announcement reversed the position that the FDA staked out in late February 2020, when it issued a guidance document for the industry on the development of IVDs to diagnose COVID-19.

The February guidance set expectations regarding the analytical and clinical validation of IVDs used to address the pandemic and included most complex LDTs intended to diagnose the disease. The FDA published a second policy in March allowing for independent authorization of LDTs by states and expounded on these policies again in May.

The FDA's oversight of LDTs in the context of COVID-19 — promulgated with little fanfare given the exigencies of the pandemic — represented yet another turn in the agency's mercurial relationship with these controversial diagnostics that dates back more than four decades. Because the administration and the Department of Health and Human Services has now rescinded the FDA's prior guidance, laboratories must decide whether to voluntarily seek an emergency use authorization from the FDA for their LDTs, which would provide the tort protections associated with all such authorized countermeasures, or to proceed without it. Longer term, the future and degree of FDA oversight of LDTs will remain uncertain until either the FDA undertakes a formal rulemaking process or Congress takes legislative action.

History of LDT Regulation

IVDs are “those reagents, instruments, and systems intended for use in 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,” according to the FDA. “Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.” The FDA began regulating them as medical devices when Congress amended the Food, Drug and Cosmetic Act in 1976 to create the comprehensive regulatory scheme providing for the risk-based medical device classification system and premarket review process that exists today. Components of IVDs, such as antibodies, specific receptor proteins, ligands, nucleic acid sequences and other analyte-specific reagents, are also subject to FDA oversight as medical devices. Most of the hundreds of IVDs on the market today have been cleared by the FDA as Class II medical devices, which are sold to laboratories across the country.

The disconnect in this area is that, at the same time the FDA developed a robust regulatory process for premarket review of IVDs, it adopted a decidedly laissez faire approach to regulation of LDTs, a subset of IVDs that are designed, manufactured and used within a single laboratory for clinical use. The FDA perceived LDTs as low risk due to their limited number and primary use in rare disease contexts. Accordingly, LDTs were not subject to the agency's robust premarket evaluations of analytical and clinical validity. Analytical validity focuses on “whether a test can accurately and reliably measure what it claims to measure,” whereas clinical validity focuses on “whether the measurement is predictive of a certain state of health.” The result is a bifurcated market, in which IVDs developed for commercial sale are held to rigorous FDA standards while homegrown tests developed for the same uses inside the developer's lab are not.

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Medical and technological advances over the past four decades have driven the development of LDTs to cover a wide range of conditions, including human papillomavirus, Lyme disease, whooping cough, certain cancers and heart disease. The growth of the LDT industry has led to concerns among stakeholders about whether current regulatory oversight of LDTs, led primarily by the Centers for Medicare and Medicaid Services (CMS), is sufficient to ensure their safety and effectiveness. Reports of inaccuracies in cervical cancer testing led to the enactment of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which extended federal regulations to all laboratories performing testing on human specimens for the purpose of diagnosis or treatment. Under the CLIA, CMS evaluates the analytical but not clinical validity of LDTs during accreditation surveys of laboratories. These surveys are conducted on a biennial basis, so it may take up to two years after an LDT has been offered for clinical use before its analytical validity is confirmed by regulators.

In July 2010, the FDA announced its intent to reconsider its long-standing policy of enforcement discretion with respect to LDTs after identifying issues with several high-risk LDTs and hosted a public workshop to gather feedback from industry stakeholders. Four years later, the FDA issued draft guidance proposing a regulatory framework for LDTs. It followed up a year later with a report on 20 case studies of potential and actual patient harm arising from inaccurate or unreliable LDTs that supported the need for increased LDT oversight. Members of the lab and diagnostic industry pushed back against the FDA's new position, asserting the FDA had no right to regulate LDTs in the first place. They argued LDTs were clinical rather than medical devices and that regulation would constitute an intrusion into the practice of medicine. Industry stakeholders were also concerned that FDA oversight would stifle innovation, raise costs for laboratories and limit patient access to LDTs they deemed vital to public health.

In January 2017, the FDA announced it would not finalize the guidance and invited Congress to address the issue. To advance the discussion, however, the FDA published a position paper synthesizing feedback it received from stakeholders as well as its own views on appropriate oversight that would balance the need for innovation with the need for assuring the safety and effectiveness of LDTs. The FDA proposed an approach in which agency oversight would be phased in over several years based on risk. The proposal would grandfather tests already on the market and exempt from most oversight LDTs that are low risk or intended for rare diseases, forensic use, public health surveillance and so-called "traditional" tests that "use components that are legally marketed for clinical use and whose output is the

result of manual interpretation by a qualified laboratory professional, without the use of automated instrumentation or software for intermediate or final interpretation." All other tests, including modified versions of grandfathered tests, would be subject over time to adverse event and malfunction reporting, premarket clearance and approval, and CLIA-based quality requirements. The FDA reserved the right to take action against any LDT, even those exempted from the phased-in requirements, in the event of deceptive promotion or inadequate validation.

Many stakeholders interpreted the FDA's announcement as a retreat to the long-standing position of enforcement discretion while it turned the issue over to Congress to resolve. The reality was less clear, however, as the agency continued to assert its jurisdiction over LDTs in certain circumstances. In October 2018, FDA issued a guidance warning that many genetic tests on the market that claim to predict a patient's response to specific medications had not been reviewed by the agency and might not be supported by requisite scientific or clinical evidence. In April 2019, the FDA issued a warning letter to Inova Genomics Laboratory alleging that its genetic tests, which were offered for the same purpose, were adulterated and misbranded, and posed a significant public health concern because they had not been adequately validated. Notably, the FDA rejected Inova's assertions that the company was operating within an "LDT Exemption" by explaining that no exemption existed and that the agency never created a "legal carve out" from its premarket review processes for LDTs. The agency also asserted that it retained the discretion to take action against LDTs "when appropriate" despite its long-standing policy of exercising enforcement discretion. The FDA's unpredictable approach toward LDTs left members of the lab and diagnostic industry unsettled and anxious about federal challenges to the legality of their tests.

Considerations for COVID-19

Facing the COVID-19 pandemic, the FDA took another step toward more complete oversight when it included LDTs in its polices for other IVDs intended to diagnose the disease. The position was no doubt fueled by the FDA's desire to ensure a measure of analytical and clinical validity for all complex tests used to diagnose the disease, given the obvious exigencies and public health equities at issue. However, the Trump administration's August 19 announcement formally rescinds guidance and other informal statements from the agency concerning premarket review of LDTs. The move frees developers of LDTs to act without FDA pre-review, which offers a measure of clarity for the market but also triggers concern from public health experts who believe now is the time for more oversight, not less.

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Congressional Action

Against this backdrop, there may be greater pressure than ever on Congress to take up the issue. Lawmakers have made several attempts at determining the future of LDT regulation. A draft bipartisan bill released in March 2017 outlined a regulatory framework for LDTs based in part on a proposal by the Diagnostic Test Working Group, a coalition of industry stakeholders. After feedback from the FDA, lawmakers unveiled a new bill, the Verifying Accurate, Leading-Edge IVCT Development (VALID) Act, in December 2018. On March 5, 2020, lawmakers introduced a revised VALID Act with bipartisan sponsorship.

The VALID Act would create a new regulatory framework to govern the development and use of all in vitro clinical tests (IVCTs), which would include both IVDs and LDTs. The proposal would replace the three-tiered system used to regulate other medical devices with a two-tiered system consisting of low- and high-risk tests (although the legislation would allow the FDA to develop special controls for certain high-risk tests, which could evolve into a third tier of moderate-risk devices). The legislation would require premarket evaluation and compliance with quality system regulations unless an exemption applied. Like the FDA's 2017 proposal, the act would exempt low-risk tests such as those intended to treat rare diseases and some LDTs that are already in use. Current LDTs not eligible for grandfathering under the act would be handled under special transitional provisions. The legislation also includes a precertification program intended to reduce regulatory burdens and provide priority review/breakthrough concepts. The program is modeled after those that exist today for other medical products to support expedited development and review of novel tests or tests intended to treat a life-threatening or irreversibly debilitating human disease or condition.

Conclusion

Whether and when Congress will act on the legislation is unclear. The current controversy surrounding COVID-19 testing is sure to put a spotlight on this issue, and the VALID Act has bipartisan support in committees of jurisdiction in both chambers. But the United States is heading toward another presidential election, and the current Congress has been notably partisan. The Medical Device User Fee Amendments must be renewed in September 2022, and that must-pass legislation is a likely vehicle for enactment of the VALID Act if it is not taken up beforehand. Some form of the legislation certainly could move in the next year, but the window is tight given the election and the other pandemic-related causes, which will take priority.

In the meantime, industry stakeholders should closely monitor developments in the LDT space. LDTs and related genetic tests play a significant role in health care decision-making, and a new regulatory framework will have major implications for the future of these products. But critical questions remain, including whether Congress will take action and whether the FDA will eventually act if Congress does not. Whether the FDA intends to respond to the August 19 announcement by initiating a rulemaking or formally modifying its 2017 position is unclear. The FDA likely will wait for the outcome of the election and take stock of its options then. Regardless of how, if at all, a more defined regulatory framework for LDTs ultimately crystallizes, the latest announcement makes clear that lasting guidance is necessary for all parties to navigate the world of LDTs with some measure of certainty, both during COVID-19 and beyond.