The Regulation of Laboratory-Developed Tests

Background

Laboratory-developed tests (LDTs) offered by clinical labs at academic health centers are not currently regulated by the FDA, although the labs themselves are subject to regulation and inspection through the Clinical Laboratory Improvement Amendments (CLIA) overseen by the Centers for Medicare and Medicaid Services (CMS). In October 2014, the U.S. Food and Drug Administration (FDA) released draft guidance on its proposed oversight of LDTs and in vitro diagnostic (IVD) tests, both of which are both designed and used by a single laboratory, using the existing device regulations. The purpose of this proposed framework was to give the FDA oversight of LDTs "based on risk to patients rather than whether [the LDTs] were made by a conventional manufacturer or a single laboratory." In this new structure, LDTs designated as higher-risk, including companion diagnostics and LDTs used to inform treatment decisions, would be reviewed by the FDA through the existing pre-market review process, and certain LDTs, including those deemed to be low-risk and those used for rare diseases, would not require the same process under the FDA's use of enforcement discretion.

In January 2017, the FDA announced that it would not be issuing final guidance on the regulation of LDTs and instead released a discussion paper[1] synthesizing the FDA's response to over 300 sets of comments to the draft guidance and setting forth its proposal for significant modifications that could be made to a future version of the agency's efforts. The document, issued in the final days of the outgoing administration, does not constitute enforceable guidance, nor is it the official position of the FDA.

Alternative Proposals

The release of the FDA guidance prompted the discussion and development of several alternative proposals from stakeholder organizations and legislators. The goals of these efforts generally tried to ensure the validity and utility of LDTs without slowing innovation, creating a burdensome and expensive process, or jeopardizing patient care and advances in personalized medicine. The alternative proposals differ in whether the FDA or CMS should bear primary responsibility for LDT oversight and also demonstrate different approaches to classifying tests based on risk. Those alternative frameworks that propose an expanded role for CMS note that LDTs, while currently not regulated by the FDA, are subject to some level of oversight through CLIA. More "CLIA-centric" proposals suggest that CMS' role should be expanded by investing additional federal resources in CMS and modernizing CLIA to give greater oversight responsibility and enforcement authority over LDTs. Some suggested a blended approach, where certain tests, such as those deemed very high risk or containing proprietary information are automatically or voluntarily submitted to the FDA for approval, while the vast majority of LDTs would either be regulated through CLIA or not subject to additional regulation.

In parallel discussions, draft legislation proposing alternative mechanisms for regulating and addressing LDTs and IVDs has been released. In October 2015 a discussion draft released by the U.S. House of Representatives Energy and Commerce Committee suggested that "In Vitro Clinical Tests" (IVCTs), which would include LDTs, would be classified based on the degree of relative harm that an inaccurate result would pose for a patient. The draft bill also discussed mechanisms for establishing analytical and clinical validity of IVCTs. An April 2017 discussion draft of the Diagnostic Accuracy and Innovation Act was released by Representatives Boucshon and DeGette, and would create a new center in the FDA called the Center for In Vitro Clinical Tests. These tests would be explicitly excluded from the Food Drug and Cosmetic Act definitions of drugs, devices, and biological products and regulated under a new framework implemented by the new center.

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

AAMC Position and Principles for Evaluating LDT Proposals

The AAMC agrees that LDTs used for diagnostic and treatment decisions should have clinical validity and accuracy. Simultaneously, the AAMC recognizes that LDTs are often an integral component of innovative, rapidly evolving, cutting-edge medical care, and shares our members' concerns that onerous regulation of LDTs could interfere with delivering this care, negatively impact patients, or mire the development of critical new tests in a costly and laborious process.

As the AAMC wrote in its comment letter to the FDA, academic medical centers and teaching hospitals that are performing LDTs every day are "on the front line of patient care and are best able to define the impact on their own institutions and their ability to treat patients with important information gleaned from clinically validated, well-proven, and carefully tailored diagnostic tests."

As the regulation of LDTs and related issues are debated in Congress, AAMC is engaged with many stakeholders and continues to advocate regarding the importance of LDTs. With the input of many AAMC-member institutions who are deeply engaged in the provision of LDTs for use with patients across the nation, the AAMC has identified key issues that must be considered and addressed in any implemented oversight of LDTs.

Key Considerations in the Regulation of LDTs

- Any revised regulatory framework must include as one goal a recognition that an overly burdensome system to review LDTs could greatly slow the rate of clinical innovation that is critical to keeping our healthcare system vital, providing care to patients, and responding quickly to emerging public health risks.
- There is no current understanding of the number of tests that would be affected by a proposed revision to the current framework, both for existing tests that would be impacted and for tests that are yet to be developed. Before a new approach is finalized, it must take into account the frequency of modification to new and existing tests, which modifications would require a new approval process, and the rate at which new tests are being developed. This information is critical to accurately estimate the federal and institutional resources needed to implement the revision without negatively impacting patient care.
- LDTs are often innovative or low-volume tests whose speed of adoption has out-paced the ability of commercial IVD manufacturers to plan and submit formal clinical trials that would be required for the FDA approval for marketing.
- Recognizing that rare diseases may require the testing of many individuals, carve-outs for rare disease tests should be based on the incidence or prevalence of disease, not on the number of tests performed.
- A system that recognizes the proven success and validity of certain tests or categories of LDTs is essential in ensuring that the nation's resources are targeted to the review of the subsection of diagnostic tests that present the most potential risk to patients. Any regulation of LDTs should include a wide range of situations under which enforcement jurisdiction or grandfathering is applied to facilitate the continued use of current well-known and well-developed tests without undue burden on the system as a whole.
- The economic impact of institutional compliance with the proposed new regulatory framework for currently administered and newly developed LDTs could be untenable, given the cost of guiding even a single test through the FDA premarket approval process. This cost would necessarily lead to institutional decisions that could limit patient access to innovative and targeted diagnostic tests.

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