



AdvaMedDx

Written Testimony

U.S. House Energy & Commerce Committee
Subcommittee on Health

Hearing: “21st Century Cures: Examining the Regulation of Laboratory Developed Tests”

September 9, 2014

Thank you, Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee for the invitation to testify at today’s hearing. My name is Andrew Fish, and I am the executive director of AdvaMedDx, the trade association representing the leading manufacturers of medical diagnostic tests. AdvaMedDx operates as a division of AdvaMed, the medical device manufacturers trade association, under the leadership of a separate board of directors.

AdvaMedDx appreciates the opportunity to submit testimony on the important topic of regulation of laboratory developed tests (LDTs). First, I will describe how current gaps in our regulatory system lead to different treatment of diagnostic tests, depending solely on whether the test is developed by a manufacturer or a laboratory and without regard to patient safety. Second, I will explain how rapid changes in the complexity, risk, and marketing of LDTs have created an imperative for new LDT oversight. Finally, I will summarize FDA’s recent proposed framework for LDT oversight and note support for FDA action from a wide variety of stakeholders, including AdvaMedDx and our member companies.

Medical diagnostic tests, often referred to as *in vitro* diagnostic, are tests performed on specimens taken from the body, such as blood, urine, saliva, or tissue. These diagnostic tests are a cornerstone of the modern health care system, providing critical information at every stage of care: screening, diagnosis, prognosis, treatment guidance, and health monitoring.

There are thousands of different diagnostics in use and billions of individual tests are performed in the United States each year, spanning many different technologies and providing essential information about a wide range of diseases and health conditions.

Molecular diagnostics is one area of diagnostics in which rapid advances are being made and also is a major factor in FDA’s decision to enforce existing regulations for LDTs. Molecular diagnostic tests detect target proteins and specific genetic sequences (“biomarkers”) to help identify disease presence, type, progression, and recurrence risk.

These diagnostic tests help clinicians tailor care to subpopulations and individuals—enabling targeted “personalized”, or “precision”, medicine. An important component of personalized medicine is the emerging field of companion diagnostics, in which a molecular diagnostic test is used to identify whether a specific drug (for which the test is a companion) is right for an individual patient.

The diagnostics developed and distributed by AdvaMedDx member companies – including advanced molecular diagnostics – are used in a variety of health care settings, including laboratories, hospitals, doctors’ offices, clinics, and the home. Diagnostics represent only about 2 percent of health care spending but influence at least 60-70 percent of health care decisions.

Summary Points

- For years, stakeholders have recognized the inadequacy of current oversight of LDTs and called for FDA to enforce existing regulations that apply to LDTs just as they do to all other diagnostics. A document is attached (Attachment A) to this testimony that notes comments from a variety of stakeholders supporting FDA action on LDTs.
- Under existing statute, medical devices include diagnostic tests. Consequently, all diagnostics—regardless of who develops them—are subject to FDA regulation for assurance of safety and effectiveness.
- In an exercise of enforcement discretion, however, FDA has long declined to enforce its diagnostics regulations with respect to LDTs because they historically were considered low risk. This means that FDA is not reviewing LDTs for safety and effectiveness and LDTs are not subject to numerous other aspects of FDA regulation designed to protect patients.
- Over time, FDA’s exercise of enforcement discretion for LDTs has become recognized by many stakeholders, as well as FDA, as a clear gap in diagnostics oversight. As diagnostics technologies and the laboratory business have evolved, even the most advanced tests – such as technically complex genetic tests that guide choices among cancer treatments – are now developed and offered by laboratories as LDTs.
- Laboratories are regulated by the Centers for Medicare and Medicaid Services (CMS) under CLIA – the Clinical Laboratory Improvement Amendments of 1988. As CMS itself has made clear, CLIA regulations are not a substitute for FDA oversight. Many critical features of FDA oversight are missing from CLIA. Furthermore, CMS does not have the expertise or resources to oversee LDTs in the same manner as FDA.
- Unlike FDA oversight of diagnostics, CLIA:
 - Does not regulate the safety and effectiveness of diagnostic tests;

- Does not require pre-market review of tests;
 - Does not require demonstration of clinical validity (whether the test is meaningful for clinical decision making);
 - Does not require systematic adverse event reporting;
 - Does not have a process for corrections or recalls.
- A test is a test—and presents the same risk for patients regardless of whether it is developed by a manufacturer or a laboratory. Potential harms to patients whose tests return incorrect results include unnecessary treatments, with their accompanying costs and side effects, and treatment delay or failure to obtain appropriate treatment, all of which lead to worse outcomes for those patients.
 - Maintaining two very different oversight mechanisms for tests that are the same from the perspective of patient safety is bad public policy, provides an opportunity to use tests in clinical settings without sufficient clinical data, and stifles investment in high quality products that can stand up to FDA review.
 - The risk-based approach to LDT regulation that FDA has set forth addresses current gaps in LDT oversight by focusing agency resources on tests that pose the highest risk to patients. At the same time, FDA appropriately recognizes the important role that LDTs can play in providing care to patients in the medical institution setting and explicitly preserves the ability of laboratories in those settings to continue innovating in the area of LDTs.

Diagnostics Regulation and Gaps in Oversight of LDTs

LDTs Subject to FDA Oversight

The 1976 Medical Device Amendments require FDA to review the safety and effectiveness of all medical devices, specifically including diagnostic tests as defined in section 210(h) of the Federal Food, Drug, and Cosmetic Act (FDCA). As a category of diagnostics, LDTs—which are tests developed solely by a laboratory for use only within that laboratory—are subject to the provisions of the FDCA and FDA regulation that require assurance of safety and effectiveness for diagnostics.

To date, however, FDA has exercised enforcement discretion for LDTs, meaning that FDA has not enforced applicable regulations with respect to these tests and has not been reviewing LDTs to assure safety and effectiveness. LDTs also have not been subject to numerous other aspects of FDA regulation that are designed to protect patients.

How FDA Regulates Diagnostics

The main elements in FDA’s review of diagnostics are analytical and clinical validity. *Analytical validity* refers to the accuracy of a test in detecting the specific characteristics that it was designed to detect – for example, the presence or absence of a particular

gene or genetic change. This is often measured by sensitivity, specificity, detection, precision, and repeatability. Sensitivity refers to how often the test is positive when the target is present, and specificity refers to how often the test is negative when a target is not present. *Clinical validity* refers to how well the target being analyzed is related to the presence, absence or risk of a specific disease or disorder. This is often measured by sensitivity and specificity. Sensitivity refers to how often the test is positive when the disorder is present, and specificity is how often the test is negative when the disorder is not present.

Assurance of both analytical and clinical validity is essential to patient safety. Under the current oversight paradigm, there is little or no transparency for doctors and patients regarding whether tests performed are FDA cleared or are unapproved LDTs, and to what extent there is adequate clinical validity data supporting the use of an LDT to make a clinical diagnosis.

CMS Oversight of LDTs is Not a Substitute for FDA

Laboratories are regulated by CMS under CLIA – the Clinical Laboratory Improvement Amendments of 1988. CMS itself has acknowledged the clear differences between CLIA oversight of laboratories and FDA oversight of diagnostic tests, noting FDA’s unique role, scope, and qualification to assure the safety and effectiveness of tests.

CLIA regulations focus on lab practices, including testing procedures, certification, and personnel. CLIA regulations do not regulate the safety and effectiveness of tests and are not a substitute for FDA oversight. Critical features of FDA oversight are not covered under the CLIA program, which regulates good lab practices and is required for all labs performing tests, including both FDA approved/cleared tests and LDTs. Furthermore, CMS does not have the expertise or resources to oversee LDTs in the same manner as FDA.

Unlike FDA oversight of diagnostics, CLIA:

- Does not regulate the safety and effectiveness of diagnostic tests;
- Does not require pre-market review of tests;
- Does not require demonstration of clinical validity (whether the test is meaningful for clinical decision making);
- Does not require systematic adverse event reporting;
- Does not have a process for corrections or recalls.

Growing Use of More Complex and High-Risk LDTs without FDA Oversight

FDA chose to exercise enforcement discretion for LDTs because historically they were typically lower risk tests with well-established test methods or used in low volume. Now, however, LDTs regularly developed and offered by laboratories encompass even the most complex and advanced molecular diagnostics – such as genetic tests that guide choices among cancer treatments or tests used in the diagnosis and treatment of common and serious or life threatening disorders. This is true not only of well-

established laboratories, but also of new companies that establish themselves as laboratories in order to offer new tests without having to face scrutiny by FDA.

The American Society for Clinical Pathology (ASCP), in 2010, summarized the challenges posed by the evolution of LDTs as follows.

“LDTs, initially used to diagnose rare diseases and conditions, were intended to be used within a single institution by physicians and pathologists actively engaged in their patients’ care. In recent years, LDTs have become increasingly more complex, and their use has expanded to assess high-risk, but relatively common diseases and conditions. However, as LDTs have begun to assume a more pivotal role in medical decision-making, they are more frequently being performed in geographically distant commercial laboratories instead of within the patient’s health care setting under the supervision of a pathologist and treating clinician. In some instances, LDTs are being marketed directly to the patients. ASCP is concerned that due to the increased application of LDTs for genetic testing and personalized medicine, the use of LDTs outside of the physician-patient context, and the development of LDTs by larger corporations, that some LDTs may not have been properly validated for their intended use, putting patients at risk for missed diagnosis, wrong diagnosis, and inappropriate treatment.”¹

The types of trends and concerns that ASCP characterized in 2010 have continued, especially with regard to genetic testing, and have likely accelerated due to an ever growing body of research suggesting biomarker-disease correlations and technology improvements and cost decreases in genetic testing.

It also is observed that laboratories promote their LDTs to a national marketplace. Specifically in the area of companion diagnostics, we understand that shortly following FDA approvals of a pharmaceutical along with its companion diagnostic, laboratories often advertise that they can perform an LDT version of that diagnostic test. While the drug is labeled to indicate use of the diagnostic to assess whether the drug is appropriate for a particular patient, an LDT version of the diagnostic is not reviewed by FDA and may have different performance characteristics or even use different technology than the companion diagnostic approved by FDA. Marketing these LDTs as companion diagnostics without FDA assurance of safety and effectiveness does not serve the public health.

Specific numbers on the development and use of LDTs are difficult to obtain because there is no required reporting of this information. Patient billing records also do not yield this information because there is no widespread billing mechanism for identifying whether the test used was FDA-cleared or an unapproved LDT. (There are initiatives using test-specific identifiers that ultimately may bring more transparency to LDT usage through payment records, but these are only in early stages.)

As of September 5, 2014, the voluntary Genetic Test Registry maintained by the

¹ *Policy Statement, Regulation of Laboratory Developed Tests* (Policy Number 10-02), American Society for Clinical Pathology, 2010.

National Center for Biotechnology Information listed 8,245 clinical tests in the U.S. (meaning the tests are being used for diagnostic purposes, as opposed to solely for research). While reporting FDA status for those tests is voluntary, just 15 of those tests report FDA approved/cleared status. Of the remainder, 1,072 tests report that they are used pursuant to FDA enforcement discretion, and there is no information regarding FDA status for the remaining 7,158. Of those tests not reporting FDA status, however, they are unlikely to be FDA approved/cleared.² Analysis of the GTR shows that the number of tests in the database has grown sharply in recent years.

FDA Must Enforce Diagnostics Regulation for LDTs

A test is a test – and presents the same risk for patients regardless of who makes it. Potential harms to patients and public health from tests that return incorrect results include unnecessary treatments with accompanying costs and side effects, treatment delay or failure to obtain appropriate treatment, unnecessary surgery, overuse of antibiotics, and overall worse outcomes than patients who received correct results.

Without further action by FDA, the current regulatory system leaves critical gaps with respect to patient safety and public health regarding the use of LDTs. A number of examples have been noted by FDA and other commentators, including the Institute of Medicine and the Centers for Disease Prevention and Control, in which insufficient clinical validation led to either harm or unacceptable risk of harm that could have been precluded by FDA review.

Just as important, the lack of comprehensive registration and listing of LDTs and mandatory adverse event reporting means that FDA, doctors, and patients alike have insufficient information to understand either the range of LDTs that are being used—and, in many cases, marketed to doctors and patients—without FDA review, or the extent to which LDTs are being used without appropriate clinical validation and consequently failing to perform as expected or advertised.

Merits of FDA’s Proposed LDT Oversight Framework

The Food and Drug Administration (FDA) has announced that it will modernize its regulation of diagnostic tests by requiring premarket review for moderate and high risk laboratory developed tests (LDTs).

While AdvaMedDx expects to provide more detailed comments on FDA’s anticipated draft guidance on LDT regulation, we commend FDA’s commitment to the thoughtful development of a risk-based LDTs oversight framework. We note key elements of the framework, including (1) a risk-based approach, phased in over a multi-year time frame; (2) notification by laboratories to ensure a transparency and comprehensive public registration of LDTs in clinical use; (3) requirements for adverse event reporting; and (4) continued use of enforcement discretion for certain types of LDTs to minimize disruption

² Information reported from the National Center for Biotechnology Information based on tests listed in the Genetic Test Registry (<http://www.ncbi.nlm.nih.gov/gtr>).

to the laboratory industry and ensure continued innovation. The approach also works to support continuity in tests, particularly in rare disease and healthcare institution laboratories testing, consistent with risk based approach.

Risk-Based Approach

AdvaMedDx has long called for FDA to modernize its regulation by ensuring risk-based regulation of all diagnostics. In its proposed framework, FDA has indicated that it will take a risk-based, phased-in approach that focuses the agency's resources on tests that pose the highest risk to patients. FDA plans to phase in this oversight over a minimum of nine years following finalization of the LDTs guidance that is anticipated in draft form soon.

AdvaMedDx principles on a flexible, risk-based approach to regulation of diagnostics recommend that, consistent with global risk assessment, risk criteria (apart from risk mitigations) include:

- Clinical use of a test (risk associated with how the test is used in the treatment of patients)—e.g., seriousness or prevalence of the condition, prevalence of condition, reversibility of intervention, or standalone use (not supplementary to other clinical information);
- Novelty of analyte (the substance that is undergoing analysis or is being measured);
- Novelty of technology;
- Experience or training of the person performing the test; and
- Factors that reduce or mitigate risk—e.g., scientific information, literature, general and/or special controls.

Higher risk tests generally comprise tests where a false result could lead to incorrect and harmful clinical management, an unnecessary invasive procedure, or failure to follow up a serious condition. Examples include most companion diagnostics, tests for cancer diagnosis, tests that directly or very strongly influence management of serious disease, and tests for serious or fatal communicable diseases. The underlying factor for determining higher risk tests is the nature of the claims made for them (i.e., intended use).

These tests are distinguished from tests where there are multiple findings used to direct clinical management and where each finding has a specific weight in disease management. They are also distinguished from most tests used to monitor already-detected and -diagnosed disease and genetic tests where the phenotype is already known and is now being confirmed genetically. These tests are also distinct from low risk, well established tests such as cholesterol, iron, and nicotine as well as urine and blood collection kits.

Notification

As a critical step to ensure transparency for FDA and the public on the availability and use of LDTs, all LDT developers must either provide a simple notification of their tests to FDA or comply with facility listing and registration requirements. Facility listing and registration will be mandatory for LDT developers who do not opt to notify FDA. LDT developers also must comply with facility listing and registration requirements once they provide a premarket submission to FDA for review of an LDT.

Adverse Event Reporting

FDA's LDTs framework would require all LDT developers to comply with medical device adverse event reporting requirements. Adverse event reporting represents a critical component of FDA's information-gathering process after it has approved or cleared a medical device for marketing. Adverse event reporting enables corrective action on problem devices and to prevent injury and death by alerting the public when potentially hazardous devices are discovered. Analyzing adverse event reporting also enables detection of unanticipated events and user errors, monitoring and classifying of recalls, updating medical device labels, and developing educational outreach. Using adverse event report data, FDA can detect problems previously unknown as well as problems with similar devices or device categories.

Manufacturers are required to report to the FDA, within 30 days, when they learn that any of their devices may have caused or contributed to a death or serious injury. Manufacturers must also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Continued Enforcement Discretion

Several categories of LDTs will be exempt from pre-market review, including low risk tests, rare disease testing, traditional LDTs, and unmet needs LDTs. These definitions and scope of categories are explicitly outlined by FDA. AdvaMedDx supports FDA's intent in continuing to exercise enforcement discretion in specific circumstances in which LDTs play a meaningful and needed role in patient care and risks to patients are minimized or appropriately balanced against patient needs even in the absence of FDA pre-market review.

Stakeholder Support

For years, stakeholders have recognized the inadequacy of current oversight of LDTs and called for FDA to enforce existing regulations that apply equally to LDTs as they do to all diagnostics. In 2008, the Secretary's Advisory Committee on Genetics, Health, and Society, in its report entitled "U.S. System of Oversight of Genetic Testing," recommended that "FDA should address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests."

Writing to the White House in 2012, 24 patient advocacy organizations called for FDA to publish draft guidance on LDT regulation. As one letter from numerous organizations stated, “The promise that advanced diagnostics hold for patients is tremendous, but, at the same time, the increasingly pivotal role of these diagnostics in patient care makes it imperative that their safety and effectiveness is assured by the FDA prior to use.”

A document is attached to this testimony that notes comments from a variety of stakeholders that support FDA action on LDTs.

Conclusion

The current diagnostics oversight paradigm results in a tremendous public health gap and highly disparate treatment of tests that are the same from the perspective of patient risk and safety, simply on the basis of whether they are developed by a manufacturer or a laboratory. This is bad public policy, provides an opportunity to use tests in clinical settings that have insufficient clinical data, and stifles investment in high quality products that are assured safe and effective for patients.

AdvaMedDx commends FDA for moving forward to address the patient safety gaps that currently exist in LDT oversight and supports the key elements of the oversight framework that FDA recently announced. We appreciate the opportunity to submit this testimony at today’s hearing and look forward to commenting in detail on FDA’s draft LDT guidance after it is published.