

The Long and Winding Regulatory Road for Laboratory-Developed Tests

Ronald L. Weiss, MD

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Upon completion of this activity you will be able to:

- describe the current regulatory framework for laboratory-developed tests (LDTs).
- discuss the Food and Drug Administration's position on the future regulation of LDTs and potential alternative approaches.
- outline past and present proposals in Congress to regulate LDTs.

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Abstract

“High complexity” clinical laboratories are approved under the Clinical Laboratory Improvement Amendments to develop, validate, and offer a laboratory-developed test (LDT) for clinical use. The Food and Drug Administration considers LDTs to be medical devices under their regulatory jurisdiction, and that at least certain LDTs should be subject to greater regulatory scrutiny. This review describes the current regulatory framework for LDTs and suggests ways in which to appropriately enhance this framework.

In his 2005 article “Health Care in the 21st Century” in the *New England Journal of Medicine*, William H. Frist, MD, then the Majority Leader of the United States Senate, wrote: “During the next decade, the practice of medicine will change dramatically through genetically based diagnostic tests and personalized, targeted pharmacologic treatments that will enable a move beyond prevention to preemptive strategies. A whole new frontier of medicine will open, with a focus on delaying the onset of many diseases such as cancer, cardiovascular disease, and Alzheimer’s disease.”¹

Five years later, Margaret A. Hamburg, MD, and Francis S. Collins, MD, PhD, the Commissioner of the Food and Drug Administration (FDA), and the Director of the National Institutes of Health (NIH), respectively, wrote in their article “The Path to Personalized Medicine”: “Researchers have discovered hundreds of genes that harbor variations contributing to human illness, identified genetic variability in patients’ responses to dozens of treatments, and begun to target the molecular causes of some diseases. In addition, scientists are developing and using diagnostic tests based on genetics or other molecular mechanisms to better predict patients’ responses to targeted therapy,” and “We [the federal government] are now building a national highway system for personalized medicine, with substantial investments in infrastructure and standards. We look forward to doctors’ and patients’ navigating these roads to better outcomes and better health.”²

There is a strong belief that personalized medicine tools, such as genetic tests, will continue the momentum toward more precise medical care and dramatic changes in how health care is delivered. As we venture down this personalized

medicine superhighway, part of the necessary infrastructure will potentially be a new regulatory framework for oversight of these patient management tests. The challenge will be in creating a framework that ensures safe travels without impeding necessary or desirable progress—that is, ensuring patient protection and innovation, without costly inertia.

In designing such a system, it is critical for policy makers and medical professionals alike to fully understand how the current regulatory structure came about. This might lend important clues about how we should proceed from this point on. It describes a superhighway that has become a long and winding road.

Current Framework for Regulatory Oversight

The 1976 Medical Device Amendments to the Federal Food, Drug and Cosmetic Act (FD&CA) gave the FDA authority to regulate medical devices, including in vitro diagnostic devices (IVDs).^{3,4} Defined as reagents, instruments, and systems intended for use in diagnosing disease or other conditions, including in determining a patient's state of health to treat or prevent disease, IVDs are packaged products developed and distributed by medical device manufacturers and sold in interstate commerce. In regulating IVDs, the FDA focuses on their safety and efficacy, the manufacturer claims about clinical "intended use" of the devices, and the quality of the design and manufacturing process.

The Act defines three classes of IVDs based on their assessment of risk to patients. Class I devices are associated with the lowest level of risk and do not require premarket review or approval before they can be used for patient care. Class II devices are associated with moderate risk to patients and are subject to general and special controls and often review by the FDA through the premarket notification, or 510(k), process. Class III devices are those of highest risk to patients and are subject to a premarket approval (PMA) process.

In contrast with IVD products, clinical laboratories perform and report laboratory tests for human patient diagnosis and management. They are regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), administered through the Centers for Medicare & Medicaid Services (CMS).⁵ Laboratories are inspected, certified, and accredited under CLIA through CMS or through independent "deemed" authorities (such as the College of American Pathologists [CAP]). CLIA focuses on the accuracy and reliability of the testing process, with attention to analytic quality control, proficiency testing, credentials of laboratory testing personnel, requirements for reporting results, and appropriate documentation of standard operating procedures. The laboratory medical director has a pivotal role in this framework. As a component of CLIA, the FDA categorizes laboratory tests

based on their level of complexity (waived, moderate, and high), on which CLIA then bases the stringency of regulatory requirements necessary for a laboratory to perform tests in each of those categories.

CLIA allows clinical laboratories to modify FDA-approved tests (so-called off-label use), and, importantly, to develop their own tests—laboratory-developed tests (LDTs)—as long as they follow the requirements to validate the performance characteristics of the LDTs. Routine, regular inspections under the auspices of CLIA are intended to ensure that these necessary steps are being followed for the LDTs offered for patient care purposes. Again, these tests are performed within the laboratory facilities themselves under the direction of expert laboratory professionals, including physicians, laboratory scientists, geneticists, and molecular pathologists. Under the CLIA regulatory umbrella, LDTs have flourished, particularly when a medically needed diagnostic is not available in an FDA-approved version. Patient care has benefited as a result.

Direct-to-Consumer Genetic Testing Has Muddied the Waters

In addition to IVD products and LDTs, we are also witnessing the rapid emergence of another important element of laboratory testing—that is, commercial companies, many with their own CLIA-certified laboratories, that offer direct-to-consumer (DTC) genetic tests. Such tests give consumers information about their own genetic markers, from physical traits (such as baldness) to certain disease associations (such as prostate cancer). The identification of these "genome-wide disease associations" has become increasingly popular among consumers.

Although, in general, these disease associations are weak to moderate at best, there is a growing list of companies offering this kind of information on an increasing number of conditions. The important distinction that needs to be made is that these tests offer "prediction" through statistical possibilities. They do not provide statistical certainties—a critical point that can easily be lost in translation in the marketing and consumer use of such products. Furthermore, *prediction* does not equal *diagnosis*. Because there are frequently so many other genetic and environmental factors that can determine whether a disease actually emerges, it is critical that consumers fully understand that the risk may never become reality. Similarly, the absence of a genetic risk factor (or the presence of a favorable one) may still not prevent subsequent development of disease. This context about the known association between a disease and genetic markers must be clearly communicated to the consumer through counseling—done best by medical professionals, particularly professionals trained in medical genetics.

The fact that many of these DTC companies develop their own tests and testing platforms has led the FDA, as well as members of Congress, to believe that these are medical devices that must be carefully regulated so that the analytic and clinical validity and clinical usefulness are clearly understood, to protect the public safety. This culminated in a series of letters from the FDA to a number of DTC genetic companies, a Government Accountability Office report entitled “Direct-to-Consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices,” and a Congressional hearing on July 22, 2010, before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce.⁶ In addition to representatives of the FDA and Government Accountability Office, witnesses included representatives from three DTC companies—23andMe, Navigenics, and Pathway Genomics. Unfortunately, the lines between predictive and diagnostic tests, as well as between IVDs and LDTs, were quickly blurred during these hearings. The danger in blurring these lines is that bone fide, clinically validated diagnostic LDTs—those ordered and used by physicians in real-world medical care—are cast in the same light as often marginally predictive genetic trait and disease associations produced by DTC genetic tests.

The Heart of the Debate Over LDTs

The FDA has considered an LDT as a clinical diagnostic test for use in the diagnosis of disease or other conditions that was developed by a CLIA-certified clinical laboratory for use in that laboratory. It is neither an analyte-specific reagent (ASR) nor a component or kit labeled for research use only (RUO). LDTs are considered mostly noncommercial (not distributed through interstate commerce to other laboratory testing sites), low-volume tests that use testing methods that are generally well-established and accessible to many clinical laboratories, performed by highly trained laboratory specialists in high-complexity laboratories, and interpreted by experts. They enter clinical practice without prior FDA review.

One central question lies at the heart of the debate over how to regulate LDTs: Are LDTs medical devices? The FDA has long taken the view that clinical laboratories act as medical device manufacturers when they offer an LDT and are, therefore, subject to the Act and the rules and requirements of FDA, including the same kind of review as manufactured IVDs. This includes demonstration that the IVD is “safe and effective” through “substantial equivalence to a predicate device” using premarket notification [ie, 510(k)], or by the PMA process. It means demonstration of analytic validity (accuracy, precision, reliability), clinical validity (clinical sensitivity, clinical specificity, predictive value), and clinical

utility (effect on clinical practice, health outcomes). Clinical utility demonstration typically requires expensive prospective clinical trials. To date, however, the FDA has used “enforcement discretion” in exerting what it sees as its legal authority to regulate medical devices. The FDA has defined enforcement discretion as when it does not enforce some or all applicable laws and regulations on certain categories of products, such as drugs, devices, and biologics. This means that the FDA has taken selective action to regulate certain LDTs and not others.

Clinical laboratories, in turn, believe that LDTs are a *medical service*, not a *medical device*, and, thus, the laboratories are not acting as manufacturers of medical devices engaged in interstate commerce. As medical service providers and not manufacturers, clinical laboratories are not subject to good manufacturing practices or to product liability claims. Instead, laboratories meet good laboratory practice standards and are subject to medical malpractice claims. Laboratories believe that CLIA is properly focused on the quality and standards of the test processes (analytic validity through accuracy and reliability) and the personnel who perform them—in effect, the critical “moving parts” of LDTs. This difference in view has set the stage for several years of dialog between clinical laboratories and the FDA. This dialog was aired during the “FDA/CDRH [Center for Devices and Radiological Health] Public Meeting: Oversight of Laboratory Developed Tests (LDTs),” held July 19-20, 2010, in Hyattsville, MD.⁷ The FDA convened this forum to hear public input from clinical laboratories, professional societies, trade associations, commercial companies, pathologists, laboratory professionals, patient advocacy groups, and any other constituencies.

Elizabeth Mansfield, PhD, Senior Genomics and Personalized Medicine Advisor at the FDA, stated in her opening remarks at that meeting that “LDTs provide value” and are a means to respond to unmet medical needs. She followed by saying that the “FDA adds value” through a risk-based system of oversight and by providing “reasonable assurances” of predictable performance, uniform manufacture, and detection and correction of malfunctions. She went on to state that the “FDA regulates tests,” not laboratories. However, from the laboratory industry’s perspective, the more important distinction is that the FDA regulates *devices*, CLIA regulates *laboratories*, and LDTs are *medical services*, not *devices*, performed in these laboratories.

As a part of the FDA’s history of regulatory vigilance over LDTs, there have been a series of draft guidance documents that help to provide insight into the FDA’s longstanding position. The first real indication of the FDA’s new intention to apply the medical device law to LDTs was the “Draft Guidance on In-Vitro Diagnostic Multivariate Index Assays (IVDMIA),” published in July 2007.⁸ This guidance recommended that entities that market diagnostics that use

an algorithm to analyze multiple data points should file an application for PMA or 510(k) approval by the FDA. Some of these IVDMA tests were the first examples of pharmacogenomic tests, and many were LDTs. As such, the guidance drew clear attention to the FDA's concerns about the intended use, safety, and clinical efficacy of these tests. This guidance also drew sharp criticism from many members of the pathology and laboratory medicine community and helped to ignite a broader and more visible debate on LDTs.

In September 2006 the FDA issued its "Draft Guidance on Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions (FAQs)." Defining ASRs as the active ingredients intended for use in diagnostic applications, the final guidance (the "rule"), issued September 17, 2007, clarified for ASR manufacturers the rules for ensuring the quality of the active ingredients of IVDs and devices used by clinical laboratories, under CLIA regulations, in LDTs.⁹ It specified manufacturer's labeling requirements and required an informative disclaimer to be used by all laboratories on the test results based on the use of ASRs. Under the ASR rule, most were classified as Class I devices, but certain uses (eg, blood bank testing for cytomegalovirus and syphilis) qualified as Class II devices, and Class III designations were applied only to ASRs used in tests for highly contagious, potential fatal infections (eg, HIV and tuberculosis) or for use in blood donor screening designed to safeguard the blood supply (eg, hepatitis and blood group antigen testing). It further clarified that an ASR would not qualify as such if the manufacturer combined it with other products (eg, other ASRs, general purpose reagents, controls) or promoted an ASR with specific analytic or clinical performance characteristics, intended use, or validation instructions. The FDA considered both of these circumstances to represent "test systems" rather than ASRs, by definition.

In 2011, the FDA issued 2 additional guidance documents that affect clinical laboratories offering LDTs. One was for "Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions," and the other was for "In Vitro Companion Diagnostic Devices."^{10,11} RUO/investigational use only (IUO) exemptions were a part of the FD&CA, so the RUO/IUO guidance was intended to clarify for manufacturers the FDA's view on the known use of these reagents in unapproved IVD products marketed for diagnostic purposes and, thus, not exempt. Manufacturers are not to label, advertise, or promote these reagents for use by laboratories in diagnostic test systems or assist laboratories in validating their use in LDTs. Furthermore, manufacturers should not knowingly sell these reagents to laboratories that incorporate them into LDTs. And, should the manufacturers become aware of such use, they should cease such sales or comply with premarket review requirements for IVDs. Though clearly directed only

at manufacturers, this guidance also serves notice to laboratories using RUO/IUO reagents in LDTs and may result in some manufacturers discontinuing selling these reagents to laboratories. The laboratory community's response to this draft guidance included a restatement of the fact that, under CLIA, high-complexity laboratories are permitted to independently validate and use test systems that are modified, FDA-approved tests, as well as those that are not subject to FDA clearance or approval, including "methods developed in house," (ie, LDTs). CLIA enables a laboratory to establish the performance characteristics of such test systems in their own facilities.

The second Guidance on Companion Diagnostics was intended to explain the possible premarket regulatory pathways for therapeutics and companion diagnostics and the need for FDA oversight of the IVD test systems developed to identify patients for whom the therapeutic, in development, is indicated for use. This includes proper labeling of the therapeutic that stipulates concomitant use of the companion IVD. Specifically, the therapeutic should be used in conjunction with the appropriate results from an FDA-approved or cleared IVD. Only under extraordinary circumstances where treatment is intended for a serious or life-threatening condition, and the risk to patient safety is such, will a therapeutic be approved without a concomitant, approved IVD. And only where a therapeutic is already approved for such use, but for which there is not an approved IVD, will relabeling be approved to include the use of the unapproved IVD until such time that the IVD is approved or cleared. In the FDA's risk-based classification scheme for devices, companion diagnostics likely represent the highest level of risk and will require the greatest amount of regulatory scrutiny.

The implications for existing LDTs used in therapeutic decision making are not clearly addressed in this draft guidance, but the assumption is that the FDA will view LDTs as medical devices requiring approval or clearance before they can become an approved companion to a drug. This will present significant challenges for laboratories that already have an LDT version of a present or future FDA-approved IVD that is package-labeled with a companion therapeutic. This is especially true if the approved IVD is restricted to an (expensive) instrument platform that the laboratory does not currently have—such as the Roche Cobas 4800 for *BRAF* V600E mutation testing and Roche's Zelboraf (vemurafenib) approved for metastatic melanoma treatment. It would be far better if the FDA specified only the analytic target of the companion diagnostic rather than an approved, specific-indication, commercial version of the test.

More generally, the FDA has continued to signal publicly that it intends to regulate all LDTs as medical devices. In its 2012 Work Plan, the FDA has indicated that it will release three draft guidance documents on LDTs.¹² The first

will describe a general framework for regulatory oversight and will “incorporate stakeholder comments and concerns.” The second will describe a data collection process (registry) for use by all LDT laboratory providers, possibly the NIH Genetic Test Registry. And, the third will compare the CLIA quality management systems with the FDA Quality Systems Regulations for IVD manufacturers and identify the gaps between the two. In public statements, the FDA has indicated that this new framework will likely require several years to implement. Once these intentions are published in the *Federal Register*, the laboratory community will certainly be prepared to respond, and the FDA has indicated that it will seek stakeholder input. However, under law, draft guidance documents do not require a formal response to public comment as does the Notice of Proposed Rulemaking. This has been a source of ongoing criticism.

How Has Congress Viewed LDTs?

Historically, there have been 2 significant legislative attempts—neither of which was passed into law—to provide an additional regulatory framework for LDTs. The first was when Senator Edward Kennedy (D-MA) cosponsored with Senator Gordon Smith (R-OR) S 736, the “Laboratory Test Improvement Act of 2007,”¹³ which would have amended the FD&CA to define all LDTs as medical devices, giving the FDA clear authority over them. It would have created a regulatory framework based on the FDA’s existing medical device classification scheme and required all clinical laboratories with LDTs to register with the FDA as device manufacturers. These laboratories would then be required to submit documentation on intended use and analytic and clinical validity for each LDT. The FDA review of these submissions could result in approval or a requirement to seek 510(k) or PMA, depending on the judged class of the LDT (II or III). The legislation stipulated that most LDTs would likely be considered as Class II devices once approved.

Taking a somewhat different approach, then-Senator Barack Obama (D-IL) cosponsored with Senators Richard Burr (R-NC) and Robert Menendez (D-NJ) S 976, the “Genomics and Personalized Medicine Act of 2007.”¹⁴ This legislation proposed a means to improve federal agency collaboration on understanding and developing a framework that would more effectively promote the use of genomics research in disease diagnosis, drug safety, and the identification of novel treatments. It would have established the Genomics and Personalized Medicine Interagency Working Group charged to “facilitate collaboration, coordination, and integration of activities within the Department of Health and Human Services (DHHS) and other federal agencies....” It would have also established the National

Biobanking Initiative, and, relevant to the debate on LDTs, it would have commissioned 2 studies. The first, from the National Academy of Sciences, would address incentives to encourage the development of companion diagnostics, and the second, from the Institute of Medicine, would study and report on recommendations to improve the federal oversight of genetic tests.

Most recently, Representative Michael Burgess (R-TX), a physician on the House Energy & Commerce Committee, introduced into the 112th Congress HR 3207, the “Modernizing Laboratory Test Standards for Patients Act of 2011.”¹⁵ Departing from the 2007 approach in the Senate to define all LDTs as medical devices, this bill would explicitly exclude LDTs from this definition, removing them from the FD&CA. At the same time, by building on the fundamental CLIA architecture, Representative Burgess and a number of key House cosponsors would provide CMS with additional authority to evaluate the clinical validity of LDTs. The current CLIA framework stops at assuring analytic validity but requires that laboratory directors ensure that their tests are of sufficient quality for patient care. The legislation further proposes to establish a Test Registry Data Bank for all LDTs and require all laboratories to notify the DHHS of all of their LDTs, to provide documentation on the clinical validity of any new LDT, and to maintain records on the clinical validity of all existing LDTs. The DHHS would be required to establish a timely review and approval process for these submissions, but laboratories can market their LDTs while the notification and review are pending. Should DHHS question the clinical validity documentation on a new LDT or have concerns about risk for immediate harm to the public, the laboratory may be ordered to cease offering and marketing the LDT. The Burgess legislation also proposes the addition of postmarket reporting and records maintenance on patient safety issues to the current CLIA framework.

For DTC testing, any entity offering LDTs directly to consumers (the test-offering entity) would have similar CLIA-based oversight, and the CMS would be empowered to sanction any test-offering entity it believes poses an immediate threat to public health. The cost to CMS to take on these additional responsibilities would be offset by increases in laboratory user fees. The fate and final language of this current legislation are uncertain, but it is supported by many in the clinical laboratory community, with improvements being offered by others. It is the first legislative vehicle to reinforce and strengthen the current regulatory framework under CLIA, avoiding duplicative oversight by another federal agency (FDA).

The outlook for congressional action this year on LDTs, related IVDs, and medical devices remains uncertain during the second session of the 112th Congress. There is clearly continued interest, however, from members of Congress and

from a wide array of public, private, and commercial constituencies. Legislation like the “must pass” reauthorization of the Medical Device User Fee and Modernization Act, which expires this year, at the end of fiscal year 2012, could serve as one important vehicle for LDT legislation.

What Is a Reasonable Framework for Oversight?

As complex technology advances, it is my opinion that there is a need for an enhanced regulatory framework for the tests of highest risk to patient care and well-being. Such a framework should incorporate the best features of CLIA’s regulatory framework for clinical laboratories, with attention to the FDA’s approach for certain diagnostic medical devices. Unnecessary duplication, particularly for inspections and for quality systems design between the two, should be avoided by using the existing CLIA framework in which to make these enhancements.

This new framework should be developed carefully, methodically, and with full stakeholder involvement so that transparency is maintained throughout. Whatever system is developed should be adopted during a carefully planned phase-in period.

The regulatory framework should apply to the new LDTs that pose the highest potential risk, while LDTs of long-standing clinical use should be “grandfathered.” Low- and moderate-risk tests should not be subject to an approval process.

Regarding the risk-based classification scheme, a third-party body of experts should be impaneled to define the risk strata and establish the criteria used for categorization of specific new LDTs. This panel of experts should be used in an ongoing manner, with criteria adaptable to emerging new technologies.

There is a need for a standardized validation process for LDTs that includes their clinical validity. Such a standard should be developed and maintained with the help of an objective third-party body of experts. This will allow for the development and independent review of LDTs in a consistent and equitable manner that mimics the scientific peer-review process.

Once validated through a more consistently applied, standardized process, LDTs should be placed on a public registry maintained by a reputable source, such as the NIH. The specifications of what each LDT’s citation should include should be the result of a consensus among all interested stakeholders. Such a registry would serve as a reference resource for the public, physicians, patients, and scientists.

Finally, this framework should be the result of multiple stakeholder meetings carried out over sufficient time to limit or reduce the unintended consequences associated with

the new framework. This is best managed through specific legislation or through the Notice of Proposed Rulemaking and Comment process, which is more transparent and publicly accountable than the FDA’s usual process for guidance documents.

Many of these critical elements are found in HR 3207 and in a number of previously proposed legislations. It should also be noted that the CAP has proposed a risk-based LDT oversight system that would represent a partnership among the CAP, CMS, and FDA, recognizing a role for the FDA in reviewing and approving high-risk LDTs.¹⁶ The CAP would assume the role of the independent, third-party body of experts and would facilitate the development of evidence-based principles of clinical validity and, through its Laboratory Accreditation Program, would inspect laboratories for compliance with LDT validation requirements.

Summary

The mapping of the human genome, in many ways, stood traditional science and biology on their heads. Scientists and medical professionals could now “see” how the primary building blocks of life fit together, and they design tools that use that knowledge in understanding disease at its most basic level. The future of human medicine, thanks to this knowledge, is shining with possibilities.

It, therefore, should not be surprising that regulatory mechanisms developed in 1976 (device regulation) and 1988 (CLIA regulation) may not fit perfectly with a science that was hardly imagined at that time. Instead, we should seek a blend of what works from these approaches, leavened further by innovative new ideas and approaches. Such a blend must mark the way forward. The entire pathology and laboratory medicine community of organizations, societies, and associations, together with other health care providers, patients, and consumers, are the key stakeholders in this effort. As such, we need to work together to release the full potential of the personalized medicine highway and do so in a way that supports patient care while facilitating timely, economical, and effective development and adoption of these technologies.

From the Department of Pathology, University of Utah School of Medicine, Salt Lake City.

Address reprint requests to Dr Weiss: Dept of Pathology, University of Utah School of Medicine, ARUP Laboratories, 500 Chipeta Way, Salt Lake City, UT 84108.

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