FDA Oversight of Laboratory-Developed Tests: Is It Necessary, and How Would It Impact Clinical Laboratories?

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In 2010 the US Food and Drug Administration (FDA)7 stated that it would issue guidance on its oversight of laboratory-developed tests (LDTs), and in July of that year the FDA held a public meeting to receive feedback on a risk-based application of LDT oversight (http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm). The FDA acknowledged that LDTs have been in existence since the Medical Device Amendments of 1976 and that historically they had exercised enforcement discretion with respect to oversight. In 2010, however, the FDA stated that the complexity and risk associated with newer LDTs were such that oversight was necessary and that the FDA has “the statutory authority to assure that devices, including LDTs, are safe and effective for their intended use.” Indeed, the FDA notice cites a 2008 report from the Secretary’s Advisory Committee on Genetics, Health and Society (SACGHS) that recommended that the FDA address genetic LDTs because of its experience in evaluating laboratory tests.

Changes in the LDT environment that have prompted the FDA to consider oversight include the increasing complexity of genetic and other ‘omics testing and the increasing number of diseases that can be diagnosed, monitored, or treated on the basis of LDT results. Because of this state of affairs, the FDA stated that the risk associated with LDTs is far greater today than in the past. Other reasons for oversight include the movement of LDTs from local hospital-based laboratories to national reference laboratories, and the existence of LDTs for analytes that currently have FDA-cleared tests in the marketplace. In addition, the FDA cites a change in business models for providing LDTs, in which corporations, instead of local hospitals and local pathologists, are responsible for providing LDTs for large numbers of patients all over the country.

The clinical laboratory industry has expressed concern that FDA oversight of LDTs will be impractical to institute, will stifle innovation of new ‘omics tests necessary for the realization of “personalized medicine,” and will place a large burden on laboratories by having 2 sets of oversight regarding LDTs, CLIA/Centers for Medicare and Medicaid Services (CMS), and the FDA. In the US House of Representatives, Congressman Michael Burgess, MD (R Texas), introduced a bill (H.R. 3207) during the 112th Congress entitled, “Modernizing Laboratory Test Standards for Patients Act of 2011” that will restrict the oversight of LDTs to CMS. This topic has wide-ranging implications for the development, validation, and regulation of new LDTs. We interview a clinical chemist and a molecular pathologist who oversee the performance of LDTs at large academic medical centers, the CEO of a large university-based national reference laboratory, and Congressman Burgess.

The FDA states that they have statutory authority and the responsibility to oversee LDTs in a manner similar to their oversight of other medical devices that are marketed by in vitro diagnostics (IVD) companies. How do you believe LDTs differ from those IVD tests currently under FDA oversight?
Edward R. Ashwood: The FDA has clear authority over food, drugs, and medical devices. I don’t consider LDTs to be “laboratory-developed tests” but instead consider them “laboratory-developed testing services.” Each LDT provided by our laboratory undergoes an extensive initial validation. FDA-approved medical devices are subjected to a less stringent method-verification process. Most often, the clinical usefulness of an LDT is determined by review of the medical literature and sometimes by clinical studies. Once in service, each LDT is subject to ongoing assessment in a patient-care environment under the supervision of credentialed laboratory directors and staff. Often, the high volume of patient testing reveals details about the LDT that initial validation cannot. About half of our R&D efforts are dedicated to improving existing LDTs.

Thomas Annesley: The majority of LDTs are developed, validated, and introduced by clinical laboratories as a service to patients, not as a commercial product. If asked whether an LDT represented a service or a reagent, the predominant answer would be as a service, i.e., the service being a test result that a treating physician uses as a component of patient care. This distinction is important in the eyes of clinical laboratories and is valid in most circumstances. Where the situation gets blurry is in the cases of 1) proprietary in vitro diagnostic multivariate index assays, which make use of multiple variable interpretation functions or special statistical programs to derive a patient-specific result or risk score; and 2) direct-to-consumer testing.

Debra Leonard: From early pathology practice, pathologists and laboratory directors have validated tests, defined interpretative criteria, and assured the quality of tests performed in their clinical laboratories. This is a pathologist’s medical practice, which does not fall under the regulatory purview of the FDA. While this may seem like a radical statement, one must consider whether FDA clearance or approval achieves better test performance and higher quality than LDTs developed under CLIA. In the SACGHS 2008 report on oversight of genetic testing, no evidence of harm from LDTs was identified, with the College of American Pathologists (CAP) presenting evidence of good performance of LDTs in their proficiency-testing programs. I have asked for a long time and continue to ask, “Where is the harm caused by LDTs?” Both FDA-approved IVDs, as well as LDTs regulated under CMS/CLIA, come to market before there is solid evidence of the clinical utility of the test (as defined by improvement in patient outcomes), which will not be addressed by bringing LDTs under FDA oversight. Stronger evidence for the clinical usefulness of tests needs to be promoted through patient-centered outcomes research. I do agree that if a test is highly complex and interpreted by a proprietary algorithm, then such tests should require FDA approval, whether sold as an IVD (which would normally go through FDA review) or performed by a company as an LDT. Specific to genomic tests, pathologists must clearly define the line between the technical aspects of genomic tests and the medical practice of interpreting the sequence results, both for regulatory-oversight purposes and for payment models.

Michael Burgess: FDA jurisdiction over LDTs has never been legally determined and remains uncertain and questionable at best. IVDs are functionally similar to LDTs but operationally very different. The components of LDTs are not marketed as kits or test systems, and they are not physically distributed or delivered outside the laboratory. Instead, laboratories provide written reports of the results to the ordering physicians after they have performed the tests. Thus, clinical laboratories that develop and perform LDTs are merely selling services to outside entities.

LDTs are not medical-device products sold through interstate commerce but are services provided to the ordering provider and offered only by the laboratory that validates and develops it. Professional medical services are not regulated by FDA. I believe a modernized CLIA will meet patient needs and ensure that these tests are not only accurate and reliable but also clinically valid. Even if LDT services were somehow considered “medical devices,” they would still not
qualify for FDA regulation. Laboratories performing these tests are engaged in a process that does not involve any sale or distribution of a medical device to a third party.

**A modification of an existing FDA-approved assay makes the assay an LDT at that particular institution. An example would be to use cerebrospinal fluid when the manufacturer does not include that sample type in its instructions for use. Should this type of LDT also be reviewed and approved by the FDA?**

**Edward R. Ashwood**: No, CMS/CLIA or a deemed agency should be responsible for reviewing a laboratory’s process for modifying an FDA-approved test.

**Thomas Annesley**: No. Existing CLIA and CAP requirements are clear that any non–FDA-approved use of an assay/method, which includes testing alternative matrices, must include validation of assay performance for that particular specimen type.

**Debra Leonard**: Modification of an FDA-approved assay absolutely requires a validation process. Under the New York State Department of Health (NYSDOH), modification of an FDA-approved test requires submission of the validation data and approval of the test by the NYSDOH. I only worry that the FDA does not have the staff to accommodate the volume of review that the inclusion of modifications would entail, which would result in a protracted review process. Also, I feel strongly that pathologists know how to validate such modifications under CLIA.

Many laboratories put a disclaimer on results from an LDT that the FDA has not cleared or approved. What does your institution do in that regard?

**Edward R. Ashwood**: Our laboratory places a compliance statement on LDTs in compliance with CAP inspection checklist requirements. For some checklists, CAP requires LDT reports to include a statement that the assay was developed by the laboratory. These statements can be reviewed at http://www.aruplab.com/CS.

**Thomas Annesley**: The following statement is added to the report: “This test was developed and its performance characteristics validated by the laboratory. It has not been cleared nor approved by the FDA.”

**Debra Leonard**: A statement is included on all Molecular Pathology Laboratory LDT reports that the performance characteristics of the test were validated by the laboratory and that the test is not FDA approved/cleared, but the statement is inconsistently added to LDT reports from other laboratory sections. Also, because the laboratory is located in New York State, all LDT tests are submitted to the NYSDOH for review and approval, although this is not stated on any of the LDT reports.

If the FDA enforces oversight of LDTs, what do you think the impact would be on academic hospital and reference laboratories?

**Edward R. Ashwood**: If the FDA enforces oversight of LDTs, academic and reference laboratories will be in the unenviable situation of double regulation, a burden that will increase cost, slow progress, and make laboratory services less safe and effective. Perhaps most importantly, patient care will be adversely impacted. Additional oversight will limit the ability of laboratories to gain clinical experience with new tests and eliminate the flexibility they need to make incremental changes to tests as new scientific discoveries emerge. Supplemental filings may take months to years to conduct and be prohibitively costly. Ultimately, there is no proof that FDA regulation of LDTs will make LDTs safer and more effective.

**Thomas Annesley**: There would be a marked impact. Consider, for example, the impact that FDA oversight would have if the existing newborn-screening assays were withheld from use while the FDA cleared each state’s assay for use. In the case of therapeutic agents, imagine the inability to optimize transplant medications until the FDA cleared an assay for monitoring immunosuppressive drug concentrations. Historically, at the time that each immunosuppressive drug has been cleared by a designated division of the FDA, the assay used to monitor efficacy in clinical trials has not received FDA approval. In other words, we have had approved drugs that required monitoring for which there were no approved FDA assays. Had the introduction of LDTs for these drugs been impacted by FDA oversight enforcement, we would have had a long wait or still be waiting for an FDA-approved test.

**Debra Leonard**: For laboratories operating in New York State, an FDA-like submission and review process already exists. Before February 2012, tests could not be performed until after approval was received from the NYSDOH review process, which often delayed initiation of testing by up to a year due to slow turnaround times on reviews from some of the testing-category sections of the NYSDOH. Since February 2012, laboratories need only to submit their validation package to the NYSDOH and can begin testing, with the need to respond in a timely...
manner to any questions or additional validation requirements from the NYSDOH review process. This process is much better for laboratories and does not compromise patient safety. Any additional requirements from the FDA would create additional work and delays for laboratories, and coordination of the required submissions with existing state requirements, such as for the NYSDOH, would be greatly appreciated.

**Michael Burgess:** Applying the FDA’s regulatory approach to LDTs is redundant, will stifle innovation, and will require additional government funds for the FDA— but can be done at no cost to the government through CLIA, if the legislation I have previously proposed is adopted. CLIA explicitly requires the laboratory director to ensure all tests and services they provide are effective for patient care. Building on the current CLIA regulatory structure—rather than starting anew with the FDA—will clarify and strengthen CMS authority for clinical validity and better protect patients, while also allowing for innovation in diagnostics that will address patient needs.

If LDTs were regulated as medical devices by the FDA, it would significantly tax an already overtaxed agency and stifle access to important tests. CLIA is a more logical, cost-effective, and efficient way to regulate. CMS under CLIA is very familiar with the oversight of the clinical laboratory industry.

CLIA has performed well in assuring that laboratories provide accurate and reliable testing services. With the growth of genetic and molecular testing in recent years, CLIA needs to be modernized to encompass new tests that were in their infancy when CLIA was last amended. My legislation put forth specific ways to modernize and strengthen CLIA to enhance the ability of laboratories to meet patient needs as well as ensure that these new tests are not only accurate and reliable but also clinically valid.

I believe without such an approach, we will threaten continued growth in one of the few sectors that are creating jobs and stimulating the economy. A recent study by the Battelle Institute found that genetic and genomic clinical laboratory testing annually generates 116,000 new jobs and $16.5 billion in economic growth.

There are numerous examples of LDTs for which FDA-cleared products are also available. Examples include mass spectrometry methods for immunosuppressive drugs or vitamin D, to name just two. Why should these assays not be under the same regulations as those marketed by IVD companies and cleared by the FDA?

**Edward R. Ashwood:** An analyte like vitamin D can be tested by a laboratory using an FDA-approved medical device or by a laboratory providing an LDT service. The FDA does not have adequate resources to inspect LDT services. If the FDA were to secure the resources, then clinical laboratories offering LDTs would be regulated by both CMS/CLIA and the FDA, creating a double burden. Turning the question around, “Why shouldn’t IVD manufacturers who offer vitamin D tests be regulated by CMS/CLIA?” shows the incongruity of the original question.

The FDA-approval history of vitamin D is fascinating. The FDA considers a vitamin D test a class II device and has assigned it the code “MRG.” Curiously, total serum cholesterol tests are class I devices. All vitamin D submissions have been 510(k), which determines if assays are substantially equivalent. The Roche Elecsys test used the Abbott Architect chemiluminescent microparticle immunoassay (CMIA) as a predicate device. The Abbott Architect CMIA and ESA Biosciences HPLC tests used the LIAISON CIA as a predicate. The ADVIA Centaur and Diazyme tests used the OCTEIA test as predicate. The IDS-iSYS EIA test used the Gamma-B 25-OH Vitamin D RIA test as predicate. The LIAISON CIA used the DiaSorin RIA as predicate. DiaSorin RIA used the INCSTAR RIA as predicate. The OCTEIA, Gamma-B, and INCSTAR tests had no predicates but were compared to pre-1976 tests using HPLC or CPBA (competitive protein binding analysis) methods. Other than to establish reference intervals, none of the submissions included clinical trials to determine clinical usefulness. The approval times for the 15 FDA submissions varied from 29 to 422 days, averaging 176 days with a median of 141 days.

**Thomas Annesley:** Because the FDA-cleared test may not automatically be the test that best meets the needs of the institution(s) that a laboratory serves. An LDT may provide an answer with greater clinical value or may analytically perform better. Let’s use cyclosporine as an example. The first commercially available assay (an immunoassay) for cyclosporine in blood had cross-reactivity with nonactive metabolites. Expanding experimental data led to consensus recommendations to monitor the active parent drug. Chromatographic and mass spectrometry–based LDTs for cyclosporine were able to provide results that fit with consensus recommendations. Over time, numerous companies developed excellent, specific immunoassays that in some cases were validated or compared against mass spectrometry.

**Debra Leonard:** An LDT performed in the laboratory where the LDT was validated has levels of performance requirements different from those for a packaged IVD test kit to be distributed and performed in laboratories across the United States that did not perform the validation. While this may seem like an
obvious statement, the level of understanding of the performance characteristics of a test is much greater for having gone through a test-development process required for an LDT than for a more “black box” IVD test. While the majority of the same issues need to be addressed during the validation, all the issues of packaging, stability during shipping, performance by laboratory staff not familiar with the test, and other issues are not as applicable to an LDT. The oversight requirements need to reflect these differences and not be a one-size-fits-all approach, as some would suggest who want the same oversight for LDTs and IVDs. LDT validation under CLIA has been working, as stated above, so there is not a need for more stringent requirements except for the highest-risk tests and those using proprietary algorithms for interpretation.

Some manufacturers have refused to sell equipment to clinical laboratories because it is marked “for research use only” (RUO). Has your institution run into this problem? If so, how have you addressed getting equipment or supplies needed for LDTs?

Edward R. Ashwood: Yes, the draft guidance for industry and FDA staff issued by CDRH/OIVD (Center for Devices and Radiological Health/Office of In Vitro Diagnostic Device Evaluation and Safety) on June 1, 2011 (issued for comment purposes only), created a reluctance of some vendors to sell RUO products to clinical laboratories. However, we believe the draft guidance ignores the fact that CLIA 1988, which regulates virtually all clinical laboratory tests, requires laboratories to validate any test that is not FDA approved or cleared. Such components are explicitly allowed by CLIA when used in LDTs. Notably, CLIA Interpretive Guidelines for §493.1291(c)(4) require laboratories reporting test results when using instruments, kits, or test systems labeled as RUO to establish performance characteristics as they would an in-house–developed test. We have worked to resolve this conflict with our vendors by using many approaches, including offering to collaborate with the vendor to hasten submission to the FDA, looking for alternative vendors, and changing methods so that RUO products are rarely used in the test.

Thomas Annesley: My institution has not yet had a situation where equipment was the issue. However, there was a recent circumstance where a company declined to sell us a point-of-care test strip because of a “research use only” restriction that was not able to be resolved.

Debra Leonard: We have not experienced this problem.

Michael Burgess: In June 2011, the FDA released “Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only.” This draft document represents a significant change in the agency’s thinking and negatively impacts both patients and manufacturers of diagnostic products and components. Fifty-four organizations, including university medical centers, hospitals, organ transplantation groups, public health laboratories manufacturers, and clinical laboratories commented. Not one thought the guidance was a good idea—every comment was negative.

As a general matter, I believe the issue of a proper update to RUO/IUO guidance is something Congress should also evaluate. I am in the process of exploring legislative options in this area.

Dr. Burgess, do you plan to reintroduce your legislation deeming oversight of LDTs to CMS/CLIA in the 113th Congress?

Michael Burgess: I have personally witnessed tremendous strides in the development of personalized medicine—determining the right treatment, for the right patient, at the right time. The laboratory industry is constantly innovating with new tests that detect and diagnose disease, as well as informing the treating physician whether a drug or biologic is an effective means of treating a particular patient.

Despite advances, changes are needed to help ensure the accuracy and reliability of these tests while maintaining the integrity of the current regulatory framework. To that end, I have previously introduced the Modernizing Laboratory Test Standards for Patients Act, which would modernize the existing statute while promoting patient interests, public health, and the economy.

Whether I will introduce the bill in the 113th Congress, a modified version or not, I will continue to work to ensure regulation in this area is based on what is best for patient care, is best for a cost-effective healthcare system, and protects public health, while at the same time promoting economic growth, innovation, and job creation.

Editor’s Note: The FDA was invited to participate in this Q&A but declined.

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