Perspective: Convergence of CLIA and FDA Requirements—A Rational Shift in the Regulatory Paradigm

Planning for Efficiencies of Data, Resources, and Timelines
Introduction

As precision medicine gains momentum, and even approaches standard of care in oncology, the laboratory tests that support these targeted treatments—whether companion or complementary diagnostic, or drug-independent—must keep pace with the new treatment developments. This imperative has led assay developers to employ an array of development options in their pursuit of the twin goals of rapid development and broad availability to laboratories and healthcare providers. Assays are being developed for clinical trial use in a variety of settings, such as university research laboratories, reference laboratories, manufacturers, and incubators, to name just a few. The options to make these tests available for clinical trial and/or subsequent commercial use also are similarly numerous. To add to the complexity and fluidity of these options, these assays must evolve in the context of an extended test development program to meet regulatory requirements at the time of launch.

Ultimately, the most important question for a diagnostic test innovator is which assay commercialization option is best from both a treatment and a business perspective, especially recognizing that companion and complementary diagnostic tests must be readily available early as well as on an ongoing basis, to have the desired impact on drug use. The laboratory developed test (LDT) approach, which has less-burdensome CLIA oversight, has proven to be the most flexible for quick, early, low-investment availability. However, looked at from the perspective of supporting widespread use and maximum access, the commercialized in vitro diagnostic (IVD) assay (usually in “kit” form) has offered the broadest accessibility over the long-term for the patient and treating physician—albeit with the added burden of satisfying FDA requirements.

Current Regulatory Landscape

Originally, CLIA governed laboratory complexity determination, personnel requirements and competencies, and testing requirements—in other words, how tests were performed in laboratories, at a time when “home brew” tests were generally simple and most complex tests were purchased as kits. CLIA’s purview has evolved and grown to include:

- More complex LDTs
- Companion diagnostic LDTs (CDx LDTs)
- Personnel competencies and results quality in compliance with ISO 15189
- Formal quality management systems as described in guidelines published by the Clinical and Laboratory Standards Institute (CLSI)
- Specified pre-analytic/analytic/post-analytic quality considerations
Similarly, in the past, FDA oversaw diagnostic tests sold in interstate commerce and regulated their performance in terms of assay regulatory classification, assay product code, assay performance, formal Good Manufacturing Practices, and premarket submissions. As the diagnostics ecosystem has expanded in recent years, with highly complex and molecular tests, drug-test combinations, and other innovations, FDA oversight processes have expanded as well and currently include:

- Formal clarification of LDT enforcement discretion
- De novo 510(k) pathway for lower risk assays with no predicate device
- Implementation of specialized CDx regulatory processes
- Availability of FDA guidance documents for validation of molecular assays
- Establishment of new and broader definitions of quality processes
- FDA premarket submission requirements for “black box” software and proprietary results-interpretation algorithms

Until fairly recently, the LDT and IVD options were very much distinct in terms of regulatory burden; choosing between them therefore tended to be an “either-or” decision. Of late, however, both of these options are experiencing a rapidly evolving regulatory environment, which is moving toward convergence—and all signs indicate that convergence will happen at a point of more defined and stringent oversight, with CLIA becoming more “FDA-like.” It is reasonable to project that before the end of 2017, CLIA and FDA oversight will overlap even more, with essentially similar goals, perspectives, and requirements. These big regulatory changes pose big questions, chief among them: what will be the impact on the regulatory plans for LDTs and IVDs and their market accessibility in a world of converged CLIA/FDA oversight, and what steps can be taken to navigate these tougher requirements while maximizing efficiencies?

**Implications for the Future of LDTs**

In October 2014 the FDA issued a Draft Guidance containing a framework for regulatory oversight of laboratory developed tests, and in April 2015, the FDA and CMS announced the formation of a Task Force on LDT Quality Requirements. The Task Force had the goal of identifying commonalities between CLIA and FDA quality requirements, which the FDA believed would (1) enable effective and efficient oversight of the burgeoning marketplace of increasingly complex and nationally marketed LDTs, and (2) ensure that these tests were accurate and clinically meaningful. Taken together, these initiatives appear to have been developed to bring LDTs under more stringent scrutiny and accelerate the journey to de facto and eventual real FDA oversight. However, shortly after the November 2016 elections, the FDA decided to delay finalizing the LDT draft guidance, ostensibly to provide time to work with stakeholders, the new Administration, and Congress to define the best approach to balance patient protection with continued access and innovation. A further important communication on the topic came in mid-January 2017 when the FDA issued a discussion paper on LDT oversight to facilitate feedback. The paper describes a new construct that fundamentally represents an easing of some of the more rigid requirements outlined in the original draft guidance and offers a potentially reasonable balance among all stakeholders. Although the paper was presented as a discussion tool rather than a proposal, it still gives some indications of future, more efficient paths toward closer oversight of LDTs without the burden of full regulatory approval.

We believe that the most important points of the discussion paper go a long way toward addressing reservations that diagnostic test innovators and laboratories have had with the initial FDA proposals:

- Focused, More Limited Oversight

The FDA now suggests it would exercise only limited oversight of previously marketed LDTs (essentially “grandfathering” them in), traditional (ie, historically performed and less complex) LDTs, low-risk LDTs, and certain other limited LDT categories. The Agency would direct its focus toward new or significantly modified high- and moderate-risk LDTs, and exercise full enforcement only for LDTs that are not analytically and clinically proven, are deceptively promoted, or present reasonable probability of causing death or serious adverse health consequences. In addition, known types of LDT modifications would be allowed without a new submission, if defined in the premarket submission with protocols and acceptance criteria. This more limited and sharply defined focus gives innovators considerably more running room to develop and, significantly, to commercialize important new LDTs.4

- Phased-In, Risk-Based Oversight

The FDA further suggests a more condensed, 4-year oversight phase-in period that would focus initially on the highest-risk LDT issues and then move on to issues of successively lower public health concern. Year 1 would cover adverse event reporting; year 2 would see increased oversight of new or significantly modified LDTs that have the same intended use as Class III IVDs; year 3 would extend oversight to Class II equivalents—all other LDTs not meeting year 2 or 3 classifications would be addressed in year 4. This new approach would provide the dual benefits of initially reducing the number of LDTs that the FDA would need to review, while giving laboratories more breathing room to understand and meet the evolved standards.4

- Evidence Standards and Quality Systems

The FDA discussion paper continues that the Agency would focus on LDT analytical and clinical validity, including publishing analytical and clinical validity data on all LDTs, whereas CMS would focus on clinical utility (ie, clinically meaningful health outcomes). Moreover, in the new construct, CLIA analytical validation data and proficiency programs, as well as literature and well-curated databases, might be usable to support FDA analytical data requirements and clinical validity. Additionally, use of third-party reviews, such as New York State’s Clinical Laboratory Evaluation Program, might be acceptable. Finally, the FDA proposes to apply its quality system requirements to LDTs, encompassing design controls, acceptance criteria for raw materials and testing, and corrective and preventive action procedures. These suggestions could help achieve the goal of allowing greater FDA oversight on matters of safety and efficacy (its natural expertise domain), while eliminating areas of dual oversight through CLIA and FDA, and more appropriately keeping decision-making about an LDT’S utility in the hands of a “consumer.”
Action Steps for LDT Innovators

The January 2017 FDA discussion paper marks a real step toward balancing the concerns of the FDA, the IVD industry, and the CLIA laboratories on maintaining and improving LDT consistency, without unduly stifling innovation. The paper proposes a clear definition of jurisdictions to reduce the earlier perceptions of duplicative efforts. It also offers a reasonable plan to address the daunting workloads of FDA review of all LDTs and inspection of laboratories for addition of LDTs. With some foresight and planning, LDT innovators can smoothly prepare for these changes and be ready when CLIA oversight and FDA regulation complete their convergence.

To achieve efficiencies under this new paradigm, the single most important factor for an LDT innovator is to account and plan for commonalities in FDA oversight and CLIA validation when mapping development work streams and creating commercialization plans. Test developers should seek these efficiencies in all aspects of LDT development and validation, and particular attention should be given to the following areas that may not have held as much importance when CLIA exercised sole oversight.

Assay design
- Design input: target performance
- Design outputs: SOPs for reagent preparation and test procedure; raw material specifications
- Design verification and validation
- Design changes: change requires, change documentation

Assay reagent manufacturing
- SOPs for reagent preparation and test procedure
- Critical raw material specifications
- Quality control of reagents prior to release for use in testing

Assay performance validation
- Study protocols and acceptance criteria
- Software
- Software development documentation—required for FDA review and CLIA laboratory inspection

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References