January 15, 2015

On January 8-9, 2015, the U.S. Food and Drug Administration (FDA) hosted a workshop to solicit public feedback on its proposed Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs). As background, the FDA formally published two proposed guidance documents to regulate LDTs in October 2014. A further FDA layer of LDT regulation, added to the existing layers of state, Clinical Laboratory Improvement Amendments (CLIA), and College of American Pathologists (CAP) regulation, has been controversial.

Some stakeholders welcome increased FDA LDT regulation, citing the expanding geographic reach of LDTs, their growing importance in disease diagnosis and therapy selection, the increasing complexity of LDTs (e.g., multiple biomarkers evaluated simultaneously), the growing use of complex algorithms in LDTs, different LDT sensitivities and selectivities associated with various biomarkers, and previous instances of patient harm resulting from LDTs launched without sufficient clinical validity verification.

Other stakeholders are strongly opposed to FDA LDT regulation, maintaining that it is unlawful, wasteful, duplicative, incapable of keeping pace with LDT development, unnecessary, and will result in increased regulatory burdens, higher costs, decreased innovation, job loss, fewer LDT choices, and diminished patient care.

Proponents of both viewpoints, as well as those existing on the continuum between these two extremes, gave presentations at the FDA’s workshop.

The workshop was structured around six topics:

1) Components of a Test and LDT Labeling Considerations;
2) Clinical Validity/Intended Use;
3) Categories for Continued Enforcement Discretion;
4) Notification and Adverse Event Reporting;
5) Public Process for Classification and Prioritization; and
6) Quality System Regulation.

This WSGR Alert highlights workshop topics and provides commentary on those thought to be of greatest interest to the firm’s clients. Transcripts and slides from the workshop may be available from the FDA in approximately one week.

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1 The FDA published its new plan to regulate LDTs in the form of two draft guidance documents: “Framework for Regulatory Oversight of Laboratory Developed Tests” (the Framework Guidance) and “FDA Notification and Medical Device Reporting for Laboratory Developed Tests” (the Notification Guidance).
2 The FDA defines an LDT “as an \[in vitro diagnostic device\] that is intended for clinical use and designed, manufactured and used within a single laboratory.” The Framework Guidance at page 5.
4 LDTs have been regulated by the Centers for Medicare and Medicaid Services under CLIA (42 U.S.C. § 263a). The FDA discusses the difference between its proposed oversight and CLIA oversight at pages 9-10 of the Framework Guidance.
5 Information regarding CAP regulation of laboratories can be found online at http://www.cap.org/web/home/?_afrLoop=2129126233521%40%3F_afrOop%3D2129126233521%26_adf.ctrl-state%3Dywpfx1ma8_4.

Continued on page 2...
Legal Authority to Regulate LDTs

Several positions were put forth regarding the FDA’s proposed regulation of LDTs. These included:

i) The FDA does not have the legal authority to regulate LDTs;

ii) The FDA has legal authority to regulate LDTs, but must do so by notice and comment, and provide an economic impact analysis, as required by the Administrative Procedure Act (APA);

iii) Regardless of whether it has legal authority to regulate LDTs, the FDA has not shown there is a need to regulate LDTs. The FDA should not regulate LDTs until such showing is convincingly made;

iv) The FDA should regulate LDTs, but only the highest-risk tests. The FDA should exercise enforcement discretion for lower-risk LDTs; and

v) The FDA should regulate all LDTs.

WSGR Comment: It is likely that the FDA’s legal authority to regulate LDTs, and separately the FDA’s proposed regulation of LDTs via guidance (instead of APA-required notice and comment), will be challenged in the courts. This could significantly delay the implementation of FDA LDT regulation.

FDA LDT Regulatory Resources

It has been estimated that there are over 11,000 different LDTs offered today, and that number continues to grow. Speakers questioned the sufficiency of the FDA’s resources to effectively regulate LDTs in a timely manner, even with a phased-in, multi-year approach to LDT regulation.

WSGR Comment: It is likely that the FDA does not currently have adequate resources to regulate LDTs. Thus, if the FDA finalizes its guidance and begins regulating LDTs, LDT FDA premarket submissions may turn into a hurry-up-and-wait scenario. Specifically, LDT providers may work furiously to meet premarket submission deadlines, only to wait for years after premarket submission to obtain approval feedback from the FDA. LDT providers factoring FDA approval into their business models as a competitive advantage should allow for this possibility.

Quality System Regulations

The FDA asserts that its authority to regulate LDTs arises under the Medical Device Amendments of 1976, and that the FDA can regulate LDTs as medical devices. Part of FDA medical device regulation includes Quality System Regulations (QSRs). QSRs formally guide the medical device creation process from design to manufacture, packaging, labeling, storage, installation, and servicing. Speakers raised questions regarding how the FDA would adapt device-centric QSRs to LDTs, and how QSRs would be grafted onto LDTs already on the market. Several speakers indicated that their companies did not have the expertise or resources to incorporate QSRs into their current and future LDTs.

WSGR Comment: It will be important for the FDA to translate “device speak” regulations into language that LDT providers can readily understand and implement. LDT manufacturers that plan to seek FDA approval (e.g., for certain Class II and Class III LDTs) should follow QSR developments closely and plan to implement QSRs in the design, development, and provision of their LDTs.

Premarket Approval, Classification, and Harmonization

The FDA intends to phase in LDT regulation based on risk, with the highest-risk LDTs (e.g., Class III medical devices) being regulated first, and Class II and I LDT regulation phasing in at a later date. Generally, Class III devices require FDA premarket approval (PMA), and Class II devices

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6 A. Pollack, “FDA Acts on Lab Tests Developed In-House,” The New York Times, July 31, 2014, available online at http://www.nytimes.com/2014/08/01/business/fda-to-regulate-lab-developed-test-kits.html?_r=0. The 11,000 different LDT test estimate is likely conservative. Additionally, the number of times these different LDTs are run yearly amounts to millions of tests.

7 See, e.g., 21 CFR §§ 820.1-200.
require FDA premarket notification via a 510(k) submission. The FDA also intends to require adverse event reporting (MDR) for certain approved devices. A number of speakers indicated that their companies did not have the expertise or resources (personnel and financial) to assemble the necessary data and documents to support FDA PMA and/or 510(k) applications, and to engage in regular MDR analysis.

Other speakers indicated that the FDA should provide additional guidance regarding how LDTs will be classified, as classification directly affects the degree of regulation. Suggested factors included: the level of patient risk associated with false outcomes, the importance of the LDT in diagnosis or treatment guidance, LDT algorithm complexity, and LDT complexity (e.g., single biomarker or multiple biomarker analysis).

Many speakers requested that the FDA publish new guidance on harmonization with CLIA regulation. Such guidance would describe where FDA regulations differ from CLIA regulations, where they overlap, and how the FDA’s LDT regulation will seamlessly mesh with and complement CLIA oversight. Several speakers indicated that checklists like those provided by CAP were useful and that the FDA should strongly consider providing these.8

WSGR Comment: The addition of QSR requirements, adverse event reporting, and premarket notification and approval requirements will require LDT providers to allocate significant additional resources towards successfully navigating FDA LDT regulatory hurdles. Many LDT providers may be unable to provide these resources (which include both financial and human resources), and therefore may cease providing LDT laboratory services. The FDA’s entry into LDT regulation could thus result in significant industry consolidation. As a result of such consolidation, LDT providers that can allocate these additional regulatory resources could be big winners and end up controlling significant LDT market share.

LDT Modifications

LDTs are extensively modified. Common modifications include introducing a different device into the LDT (e.g., moving from one next-generation sequencing platform to another); introducing new or substituting investigational use only (IUO) or research use only (RUO) reagents into the LDT; modifying the LDT’s algorithm; adding, deleting, or switching one or more biomarkers; and changing the sample input or method of sample preparation. As currently envisioned, the FDA would require new premarket submissions for at least some of these modifications.

WSGR Comment: When LDT modification triggers a requirement for a new premarket submission is a contentious issue. Also, some LDT modifications will result in significantly improved test performance (e.g., improved selectivity, sensitivity, or both). When this happens, and two approved tests for the same diagnosis or therapeutic guidance have very different performance characteristics, it is unclear how the FDA will respond (e.g., will the FDA withdraw approval for the inferior test, or will it rely on market forces to migrate to the greatly improved LDT?). LDT providers should account for potential regulatory and market fallouts from proposed test modifications.

LDT Exemptions and Multisite LDTs

In its draft guidance published in October of last year, the FDA proposed continued enforcement discretion (e.g., exemption from premarket review and QSRs) for i) traditional LDTs and ii) LDTs for rare diseases. One factor used to determine whether an LDT is “traditional” is that the test results are interpreted by qualified laboratory professionals without the use of automated instrumentation or software for interpretation. Several speakers urged the FDA to recognize the ubiquitous nature of computers and algorithms in LDTs and mitigate or do away with this factor. Other speakers took the opposite view, maintaining that any LDT that relies on a computer algorithm should be subject to stricter FDA oversight.

As drafted, the FDA’s guidance for rare diseases characterizes these tests as meeting the definition of an LDT and the definition of a humanitarian use device (HUD). In practice, the HUD requirement limits an LDT test to being run less than 4,000 times per year. Multiple
Highlights and Commentary from the FDA’s Public Workshop …

Continued from page 3...

speakers suggested this was the wrong metric, and that the FDA adopt one or more alternative metrics, such as the metric used to determine an orphan drug (i.e., affects less than 200,000 people in the U.S.) or the frequency of a disease in the population.

Speakers also commented on unmet medical need LDTs. One proposal under consideration is that when a first unmet medical need LDT is approved by the FDA, unapproved LDTs for the same unmet medical need would be removed from the marketplace. Some speakers praised this approach for rewarding LDT providers for clinically validating their test, while others cautioned that it would create a monopoly and drive up testing costs.

Finally, speakers recommended that if the LDT owner practiced at multiple sites, once an LDT was approved for one site, the approval should be sufficient for all sites to practice the LDT.

WSGR Comment: The scope of the exemptions will be important. Broader exemption scopes will mean more enforcement discretion for (minimally regulated) LDTs. Because the FDA is concerned about clinical validity, the FDA will likely make the exemptions as narrow as possible, consistent with allowing for the continued development and deployment of rare disease and unmet medical need LDTs. The unmet medical needs proposal, if enacted, could create a competitive advantage for companies working in this area. Should the FDA adopt the position that a first approval removes unapproved LDTs from the marketplace, the first FDA-approved tests will have a significant ability to capture and retain market share.

Conclusion

Regulation of LDTs is complex, evolving, nuanced, and multi-layered, as it involves state law, CLIA oversight, CAP accreditation, and (potentially soon) FDA regulation. Companies will likely need to dedicate significant resources to achieve compliance with FDA LDT regulations. Additionally, for companies marketing or planning to market LDTs for profit, patent protection (including patent term extension) and post-grant patent challenge should be considered as part of an overall strategy to protect intellectual property and maximize market share. Finally, companies should use regulation as a tool to optimally position LDTs for reimbursement (e.g., from government agencies such as the Centers for Medicare and Medicaid Services and private insurers).

For assistance in any of these areas, or in formulating a comprehensive LDT plan, please contact David Hoffmeister, Vern Norviel, Charles Andres, or any member of Wilson Sonsini Goodrich & Rosati’s FDA or patents and innovation strategies practices.