Regulating Disruptive Technology:

FDA's Evolving Oversight of LDTs and Genetic Testing

A GenomeWeb Primer

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After several years of public debate and deliberation, the Food and Drug Administration last October took active steps toward regulating laboratory-developed tests, a responsibility that has historically been under the purview of the Centers for Medicare and Medicaid Services through the Clinical Laboratory Improvement Amendments.

LDTs — tests that are designed, manufactured, and used within a single lab — include basic diagnostics that are performed in thousands of labs across the country, but also encompass complex multigene tests that are performed in only one location and often rely on proprietary algorithms. The advent of next-generation sequencing and other genomic technologies has driven rapid growth of these highly specialized tests, while also presenting a regulatory challenge.

While the FDA has always claimed it has the authority to regulate LDTs, it has long exercised "enforcement discretion" over them. As long as such tests remain under CLIA regulations, they do not need to meet stringent regulatory requirements, such as premarket review and adverse event reporting, that are required for FDA-approved *in vitro* diagnostics. While this system worked for many years because most LDTs were considered low-risk tests, the complexities of modern tests and technologies led the FDA to determine that CLIA regulations were no longer adequate to ensure the safety and effectiveness of LDTs.

In its draft guidance on regulating LDTs, released in October, the FDA proposed a risk-based regulatory framework. The agency plans to continue to exercise enforcement discretion for Class I devices, as well as for LDTs for rare diseases and for unmet medical needs. For Class II and Class III LDTs, or moderate- to high-risk tests, FDA will phase in registration, listing, adverse events reporting, as well as 510(k) and premarket review requirements, over a nine-year period.

The FDA's draft guidance has in many ways pitted labs and IVD manufacturers against one another. Diagnostic manufacturers who have submitted tests (i.e.; companion diagnostics for personalized drugs) for premarket review with the FDA have said the current regulatory framework allows labs to take a less rigorous path under CLIA and launch competing tests. Labs, however, have countered that any improvements to regulation should be made under CMS, and that FDA oversight would lead to duplicative requirements. Clinical labs have maintained that they provide testing services, not devices; while pathologists have claimed that their work falls under the practice of medicine and is beyond the scope of device regulations.

GenomeWeb has prepared this primer to provide an overview of the events leading up to the FDA's decision to regulate LDTs, as well as some of the issues surrounding that decision. The timeline that follows is based on GenomeWeb's reporting over the last several years. We've also included an exclusive report on a new effort by several industry players to propose an alternative to the FDA's plan. The primer closes with a list of resources and our reports on the topic for readers who would like to explore the issue further.

FDA's Evolving Stance on LDTs and Genetic Tests: A Timeline

1967 The US government enacts the Clinical Laboratory Improvement Act of 1967, which establishes licensing standards for clinical labs.

1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act set forth a three-risk classification system for medical devices for human use and outline the level of FDA regulation required for devices in each class.

1988 Based on reports finding existing regulations to be insufficient, the government enacts the Clinical Laboratory Improvement Amendments of 1988. The regulations, formally published in 1992, address the complexity of testing performed at labs, certification and personnel requirements, proficiency testing, management of results, and quality assurance. The Centers for Medicare & Medicaid Services are responsible for overseeing the CLIA program.

1992 FDA first characterizes LDTs as devices in a draft guidance on research-use only products. The agency states that it can regulate LDTs, or homebrews. Labs immediately object.

1997 Despite industry opposition, FDA publishes a final rule on the use of analyte-specific reagents in *in vitro* diagnostic products and tests developed within labs. The rule imposes restrictions on how ASRs are sold and used when they are part of LDTs or IVDs.

2006 FDA issues draft guidance on *in vitro* diagnostic multivariate index assays, in which it seeks to regulate complex tests that utilize proprietary, or "black box" algorithms. The agency defines an IVDMIA as a "test system that employs data, derived in part from one or more *in vitro* assays, and an algorithm that usually, but not necessarily, runs on software, to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease."

2007

After a contentious public meeting, FDA issues a revised draft guidance on IVDMIAs. The agency asks Genomic Health to discuss the regulatory status of its breast cancer recurrence test Oncotype DX, which falls into the IVDMIA category. Meanwhile, Agendia garners 510(k) clearance for the first IVDMIA, its breast cancer recurrence test MammaPrint.

2008

Genentech submits a Citizen Petition asking the FDA to make IVD regulations more consistent by extending oversight of LDTs. The HHS Secretary's Advisory Committee on Genetics, Health, and Society issues a report with similar recommendations. Laboratory Corporation of America receives an FDA warning letter for marketing its OvaSure ovarian cancer test without sufficient clinical validation.

2010

June: The FDA states in a Federal Register notice that it is reconsidering its longstanding policy of "enforcement discretion" over LDTs. The agency decides against piecemeal regulation of LDTs and decides not to finalize the IVDMIA guidance.

June: FDA warns labs marketing genetic tests directly to consumers — Knome, 23andMe, Decode Genetics, Navigenics, and Illumina — that they are selling unapproved diagnostic devices. Congress holds a meeting to discuss a Government Accountability Office report that found test results from DTC firms were "misleading and of little or no practical use."

July: A meeting is held to garner public input on the FDA's proposal to regulate LDTs. Labs express concerns about regulation stifling innovation, while IVD manufacturers claim they face unfair competition from labs that bring tests to market with no regulatory burden.

2011

June/July: FDA issues draft guidelines on the development of companion diagnostics and a separate set of guidelines on the development and marketing of research-use only and investigational-use only IVD products. In the latter, the agency controversially places the onus on RUO/IUO manufacturers to ensure that their customers aren't using these products in the clinical setting.

October: Texas Congressman Michael Burgess introduces a bill called the "Modernizing Laboratory Test Standards for Patients Act," which would expand CMS's regulatory authority by granting it the ability to assess whether marketed LDTs are "clinically valid."

2012

April: Members of the House Committee on Energy and Commerce's Subcommittee on Health send FDA a letter expressing concerns about its RUO draft guidance. The legislators question FDA's decision to regulate RUO products based on "actual use" instead of "intended use."

July: DTC genomics firm 23andMe submits 510(k) application for its personal genome service.

2013

June: Speaking at ASCO, FDA Commissioner Margaret Hamburg asserts FDA's authority to regulate LDTs, noting that tests with insufficient validation have the potential to harm patients.

June: The American Clinical Laboratory Association files a Citizen Petition stating that LDTs are services and not devices. In the document, the lab group also challenges the agency's authority to regulate LDTs.

August: Nine Democratic members of Congress ask the Obama Administration to release FDA's draft guidance on the regulation of LDTs.

November: FDA issues final RUO/IUO guidance.

November: FDA warns 23andMe it must stop marketing its DTC genomic test because it has failed to address the agency's questions about the clinical and analytical validity of the product.

December: FDA clears first NGS instrument, Illumina's MiSeqDx, along with three assays: two for cystic fibrosis and another that allows labs to develop their own tests on the system.

2014

July: FDA notifies Congress of its intent to release draft guidance on LDTs, and issues final guidance on companion diagnostics.

September: the House Energy and Commerce Committee's subcommittee on health questions FDA and industry players on the agency's LDT regulatory plan.

October: FDA releases draft LDT guidance for public comment. The document includes a footnote that tests marketed directly to consumers aren't addressed under the framework.

November: ACLA hires a legal team to advise it on LDT regulatory matters.

January: FDA hosts a public meeting to gather input on its risk-based regulatory framework for LDTs. The input from the lab industry is largely unfavorable.

January: ACLA lawyers issue white paper laying out legal arguments for why FDA lacks the authority to regulate LDTs and makes the case for the agency to proceed with notice-and-comment rulemaking rather than the guidance track.

January: The House Energy and Commerce Committee releases a 400-page draft document containing numerous proposals for modernizing clinical trials, improving data-sharing efforts, and streamlining efforts within public health agencies. The document contains language on regulation of devices and contains a placeholder for a section on regulation of LDTs.

February: FDA hosts a public meeting on the regulation of next-generation sequencing tests. At the meeting, FDA officials acknowledge that the agency is ill-equipped for the rapid changes in sequencing technologies.

2015

February: FDA clears the first test for 23andMe's DTC genomics offering: a test for Bloom syndrome. As part of the authorization, the agency says it is classifying carrier screening tests as Class II and intends to exempt similar devices from premarket review.

March: The FDA, AACR, and ASCO co-host a workshop to discuss the challenges of standardizing companion diagnostics development when there are multiple drugs in the same class and many tests that gauge the same analyte.

April: A small group of labs and IVD developers forms the Diagnostic Test Working Group, which proposes a new category for the *in vitro* clinical test (IVCT), which would comprise both test kits and platforms, as well as laboratory test protocols. IVCTs would be a new category under the US Federal Food, Drug, and Cosmetic Act and wouldn't be overseen as devices, drugs, or biologics.

April: FDA and CMS form a task force to coordinate the two agencies' oversight of LDTs. The FDA/CMS Task Force on LDT Quality Requirements will identify commonality between FDA's quality system regulation and CLIA requirements; clarify responsibilities for labs that have to meet requirements for both FDA and CMS; and manage resources so labs aren't subject to duplicative regulations.

Small Group of Labs, Dx Firms Float Alternative to FDA LDT Guidance

April 17, 2015 | Turna Ray

Is it possible to craft a framework for regulating diagnostics that pleases everyone? A small group of labs and test manufacturers has taken a shot at it by coming up with its own proposal for regulating so-called *in vitro* clinical tests that it hopes will be an acceptable compromise for industry players that often disagree on the regulation of laboratory-developed tests (LDTs).

According to multiple anonymous sources with firsthand knowledge of the effort, the participating organizations include Becton Dickinson, Roche, Mayo Clinic, LabCorp, and ARUP Labs.

After the US Food and Drug Administration last year issued a controversial draft proposal for regulating LDTs, labs represented by the American Clinical Laboratory Association and pathologists who are part of the Association for Molecular Pathology said the agency's plan wasn't in line with how these groups contribute to healthcare. Labs said they were providing testing services, not manufacturing devices; while pathologists similarly said that their work was the practice of medicine and out of the scope of device regulations.

The new proposal by the so-called Diagnostic Test Working Group (DTWG), available here, tries to address these concerns and align regulations closer to real-world practice. The group's plan creates a new category for the *in vitro* clinical test (IVCT), which would comprise both test kits and platforms, as well as laboratory test protocols. IVCTs would be a new category under the US Federal Food, Drug, and Cosmetic Act and wouldn't be overseen as devices, drugs, or biologics, according to a draft of the plan.

Moreover, depending on a lab's or manufacturer's activities, regulation would be spread over the Centers for Medicare & Medicaid Services, FDA, and the states. IVCT design, development, validation, platform manufacturing, and preparation of materials (such as reagents) for use at more than one lab or entity would be under FDA's aegis. CMS would have jurisdiction over typical lab activities, such as preparing reagents intended for use at a single lab, developing lab operating procedures, the pre-analytical process, performing an IVCT, and reporting the IVCT results. Finally, the states, which traditionally have had authority over the practice of medicine, would continue to look after interpretation of test results and consultation with medical professionals.

According to sources familiar with the DTWG proposal, it was drafted by Ralph Hall, a partner at the law firm Leavitt Partners and an expert on FDA regulation. Representatives from the labs and manufacturing firms that participated in putting the plan together did so with the caveat that their participation doesn't mean the companies would ultimately support it. Small or single-source labs, proprietary labs, and drug companies were not part of this drafting process. However, the DTWG plans to involve them in later iterations of its proposal, according to sources.

Industry observers have noted that the DTWG's proposal may sit better with lab and manufacturing groups than FDA's LDT draft guidance. "In our view, this proposal is an intriguing start towards a potential LDT compromise," Jeff Gibbs, an expert on FDA-related legal matters at the law firm of

Hyman, Phelps & McNamara, and Allyson Mullen, a lawyer specializing in device and diagnostic regulations at the same firm, wrote in the *FDA Law Blog*.

"There are certainly many areas of clarification and development that are still required and many key details will still need to be worked out," they said. "We expect that many laboratories will prefer the DTWG's proposal as it would mean less onerous regulation compared to FDA's proposed LDT framework."

Historically, the FDA has exercised "enforcement discretion" over LDTs, leaving oversight to CMS under the Clinical Laboratory Improvement Amendments. But the agency has long felt that CLIA regulations weren't sufficient to address increasingly complex tests that were being developed and widely marketed by labs. As such, despite pushback from labs, the agency has decided to phase in all LDTs under its oversight in a risk-based manner.

Under its plan, the FDA plans to continue to exercise this discretion for Class I devices, as well as for LDTs for rare diseases and for unmet medical needs. Labs performing these tests will not have to submit them for premarket review, but will have to register and list them. For Class II and Class III LDTs, or moderate- to high-risk tests, FDA will phase in registration, listing, adverse events reporting, as well as 510(k) and premarket review requirements. It hopes to prioritize oversight of tests with the same indication as FDA-approved companion diagnostics, as well as screening tools meant to be used in asymptomatic patients and high-risk diagnostics for infectious diseases.

In contrast, "the premise of the DTWG's proposal is that the FDA's device regulation, which can't be changed except for by law, doesn't suit diagnostics," Amy Miller, executive VP of the Personalized Medicine Coalition, told GenomeWeb. "When the FDA drafted its framework, it was constrained by law. This working group was not constrained by law, so they started with the premise that device regulation just doesn't fit diagnostics, no matter where they come from. And it doesn't fit the rapid rate of change in diagnostics in terms of the modifications that must be done to diagnostic tests."

In some ways, the FDA's draft guidance has pitted labs and manufacturers against one another. Diagnostic manufactures who have submitted tests (i.e.; companion diagnostics for personalized drugs) for premarket review with the FDA have said the current regulatory framework allows labs to take a less rigorous path under CLIA and launch competing tests. Labs have countered that any improvements to regulation should be made under CMS, and that FDA oversight would lead to duplicative requirements.

The DTWG's proposal tries to ameliorate the differences among industry players and unite them under one workable plan that addresses the sticking points for different players.

"The existing regulatory structure, under which regulatory requirements are tied to the type of entity (i.e. a manufacturer or a laboratory), will be replaced by a construct under which the type and level of regulation is based on the activity being performed, regardless of the type of entity performing that activity. All entities performing the same activities will be regulated equally," the group said in a document summarizing its proposal.

For example, the same requirements will apply to a lab when developing an IVCT for distribution to another facility as apply to an IVD manufacturer that develops an IVCT for distribution, the group added.

The framework also proposes specific resources to CMS and FDA to help them carry out their regulatory responsibilities. It includes the creation of a new FDA center with "exclusive jurisdiction" over all test development activities, and proposes that CLIA regulations be modernized under CMS. The DTWG plan also keeps more or less intact certain aspects of the current regulatory system that seem to be working. An advisory panel would determine the risk an IVCT poses to patients' health under similar high-, moderate-, and low-risk categories. Labs with high-risk tests would have to establish analytical and clinical validity and submit information to obtain approval from the FDA before commercialization. Labs with moderate-risk tests would have to submit evidence on analytical validity and information to support "reasonable belief of clinical validity," but FDA may request additional information in the post-market setting. Providers of low-risk tests would not have to submit premarket data but notify the agency about the test 10 days after commercialization.

Industry representatives have criticized FDA for setting its evidence bar for diagnostics too high. In the proposal, DTWG states, "It is presumed that clinical trials are not needed to demonstrate analytical validity or clinical validity." The plan would allow labs and manufacturers to submit data from published literature, as well as a range of other evidence. The FDA can reject a submission and ask for more data but will have to defend this request based on scientific criteria and make the request in writing from a high-ranking agency official.

Labs have also expressed concern that the FDA's proposal would mean they would have to inform the agency of every tweak they make to their lab processes. This worry is lifted in the DTWG proposal since lab processes would remain under CLIA. However, test developers would need to submit information to the FDA if they modify a high-risk or moderate-risk test and that modification changes the test's intended use or a patient's diagnosis or therapeutic strategy.

Under FDA oversight, labs would be required to report death or serious injury that occurs due to a faulty IVCT. The DTWG plan would also have a system for tracking adverse events when death or serious injury is caused by an IVCT error, but the drafters of the proposal specify that an error in lab operations (i.e.; human factor issues) isn't due to a faulty IVCT and will be managed under CLIA.

Finally, in keeping with the spirit of aligning the interests of the lab and manufacturing communities, the DTWG proposal would offer incentives, such as priority review vouchers and protections for lab-manufacturer collaborations.

The DTWG plan reads a lot like legislation and that's no accident. The group has presented its proposal to the US Senate Committee on Health, Education, Labor, & Pensions, as well as the House Energy & Commerce Committee staff spearheading the 21st Century Cures initiative. Sources said that legislators are interested in the DTWG proposal because it dovetails with their interest in writing bills related to FDA and NIH issues.

Resources

FDA Resources Related to LDTs and Companion Diagnostics

November 25, 2013: Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Guidance for Industry and Food and Drug Administration Staff

August 6, 2014: In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff

October 3, 2014: Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

October 3, 2014: Draft Guidance for Industry, Food and Drug Administration Staff and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)

January 8-9, 2015: Webcasts and Transcripts from Public Workshop, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)"

Recent GenomeWeb Reports on FDA's LDT and Genetic Testing Regulation

April 21, 2015: FDA, CMS form Interagency Task Force to Coordinate LDT Regulation

March 25, 2015: At CDx Harmonization Meeting, Drugmakers Take First Step Toward Exploring Test Differences

February 23, 2015: At Public Meeting, FDA, Stakeholders Discuss Unique Challenges of Regulating NGS Tests

February 16, 2015: Regulatory Uncertainty Causing Retesting Confusion for Patients Considering New Ovarian Cancer Rx

January 28, 2015: At PMWC, FDA Commissioner Hamburg Discusses LDT Regulation, Personalized Medicine Advancements

January 15, 2015: Q&A: ACLA Lawyers Clement, Tribe Discuss FDA's Legal Problem in Regulating LDTs

January 15, 2015: Q&A: Lawyer John Conley Counters Lab Industry Arguments against FDA Regulatory Authority over LDTs

January 12, 2015: Stakeholders Ask FDA to Educate Labs on Agency Thinking, Terminology Before Finalizing LDT Guidance

January 9, 2015: At Workshop, Labs Tell FDA to Let them Tweak LDTs; Give Their Take on Labeling and Clinical Validity

December 30, 2014: Q&A: FDA's Alberto Gutierrez Fields Questions on Evolving LDT, CDx Regulations