FDA Regulation Of Laboratory Developed Tests: A Long Saga

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Law360, New York (December 15, 2016, 2:17 PM EST) --

The U.S. Food and Drug Administration’s approach to laboratory developed tests (LDTs) has had more plot twists than — and has gone on nearly as long as — some of TV’s most popular soap operas. In the latest turn of events, which aired shortly after the 2016 elections, the FDA announced that it would not be issuing final guidance documents that would have regulated LDTs as medical “devices,” and the laboratories performing them as medical device “manufacturers.”

Rather, according to an agency spokesperson, the agency has realized “just how important it is that we continue to work with stakeholders, our new Administration, and Congress to get our approach right” and plans to “outline our view of an appropriate risk-based approach in the near future” in order to “help guide continued discussions.”

If you are just tuning in now, what follows is a brief recap of the past several decades, as well as prognostication on what the 2017 viewing season may bring.

The main characters in this drama are, on the one hand, the FDA, and, on the other, the laboratory developed test or LDT. The FDA has never defined the term LDT in regulation, but uses it to refer generally to a wide range of analytical methods used by clinical laboratories to interpret patient specimens, typically at the request of a health care provider.

Some LDTs are simple, easy to perform and interpret, and yield results whose clinical meaning is well-established. Others involve novel and complex test methods and interpretive approaches, and yield results that may be clinically ambiguous or for which consensus is lacking.

In the aftermath of the Human Genome Project, the number of clinical laboratories and clinical tests performed has expanded exponentially, as has interest in using genetic and other biomarkers to customize patient care (i.e., “precision medicine”). As the cost and time to sequence large segments of DNA has plummeted, “next generation sequencing” has increasingly been integrated into clinical laboratory testing methodologies.

The FDA’s interest in regulating clinical laboratories and the tests they perform has similarly grown over time. Initially, following the passage of the Medical Device Amendments of 1976, the agency took the position that the activities of clinical laboratories fell within the “practice of medicine” and therefore...
were outside its purview. Thus, it exempted clinical laboratories — along with other health care entities that used medical devices to provide a clinical service to the public — from registration as device establishments, stating that “the Commissioner believes that full service laboratories and similar establishments are exempted from registration.”[1] This exemption remains on the books.[2]

Notwithstanding this exemption, beginning in the 1990s the FDA began to assert jurisdiction to regulate LDTs as medical devices, while at the same time exercising what in regulatory parlance is termed “enforcement discretion,” (i.e., the discretion to not enforce a particular requirement or requirements).

In 1997, the FDA explained that enforcement discretion was the appropriate approach to LDTs, recognizing that “use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances” and that “significant regulatory changes in this area could have negative effects on the public health.”[3] The agency stated that it would focus instead on ensuring that the instruments, reagents, and other tools used by clinical laboratories to develop LDTs were regulated appropriately for their intended use.

Since the late 1990s, the FDA has grappled with LDT regulation in fits and starts, often in response to a newly-emerging category of tests that the agency perceived as threatening the public’s health, and until recently at least, without a clearly-articulated vision for LDT oversight or the legal basis for the agency’s asserted jurisdiction. In only one case since 1997 has the FDA used notice and comment rulemaking to effect a regulatory change to LDT oversight.

The following table summarizes the last two decades of FDA regulation, or non-regulation, of LDTs:

<table>
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<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>April 2000</td>
<td>The FDA, through notice and comment rulemaking, regulates OTC Test Sample Collection Systems for Drugs of Abuse Testing as Class II medical devices.</td>
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<tr>
<td>Sept. 2006</td>
<td>The FDA issues a draft guidance document describing the agency’s plan to regulate a newly-defined category of laboratory test, the “in vitro diagnostic multivariate index assay” or “IVDMIA”.</td>
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<td>July 2007</td>
<td>The FDA issues revised IVDMIA draft guidance seeking to address criticisms of initial draft.</td>
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<tr>
<td>Oct. 2007</td>
<td>The FDA issues a warning letter to Exact Sciences regarding the colorectal cancer detection test PreGen-Plus, stating that the test was not an LDT subject to enforcement discretion and was being unlawfully marketed.</td>
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<tr>
<td>Sept. 2008</td>
<td>The FDA issues a warning letter to Laboratory Corporation of America regarding the ovarian cancer detection test OvaSure, stating the test was not entitled to enforcement discretion and was being unlawfully marketed.</td>
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<tr>
<td>June 2010</td>
<td>The FDA announces that it will delay indefinitely the release of a final IVDMIA guidance and instead will propose a comprehensive framework for LDT oversight.</td>
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<tr>
<td>July 2010</td>
<td>The FDA holds a public meeting announcing the agency’s plan for a comprehensive framework for LDT regulation.</td>
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In short, the FDA has proposed much but implemented relatively little in terms of LDT regulation. At the same time, the specter of regulation, and the numerous public meetings, draft guidance documents and agency pronouncements have resulted in the expenditure of significant stakeholder resources to either stave off or encourage (depending on the stakeholder’s point of view) definitive FDA action.

The FDA has exerted relatively sustained oversight over “direct to consumer” (DTC) LDTs (although the agency has never actually defined the parameters of “direct to consumer”). Since 2010, the FDA has taken the position that LDTs offered DTC are medical devices and are not eligible for FDA enforcement discretion.

The FDA has sent numerous warning and untitled letters to entities offering such tests, most notably the agency’s 2013 warning letter to 23andme. The agency subsequently permitted 23andme (and other clinical laboratories who could meet the specified requirements) to offer DTC carrier testing for a limited subset of autosomal recessive disorders.

The FDA’s recent — and largely unexpected — decision just two weeks after election day was no mere coincidence. Pursuant to a provision contained in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), the agency would have been required to notify Congress 60 days before issuing the guidance documents.

Following the election, the American Clinical Laboratory Association (ACLA), the most vocal opponent of LDT oversight, wrote a letter to Vice-President-elect Pence expressing “grave concern” regarding the FDA’s plan to issue final LDT guidance, citing the “widespread harm” to industry, patients, and clinicians that would be wrought by such action, as well as the “chilling effect on diagnostic innovation.” Given that both the House and Senate now both have Republican majorities, and the imminent change in leadership of both the Department of Health and Human Services and the FDA, the guidance documents would likely have faced significant opposition from both the executive and legislative branches.

But while the 2016 election results may have been the proximate cause of the FDA’s sudden about-face, and regardless of one’s stance on the benefit to the public from appropriately-tailored LDT oversight by government or private-sector actors, the agency’s particular approach to LDT oversight has from the outset been seriously flawed both substantively and procedurally. Indeed, had the FDA proceeded to issue the final guidances they likely would have been challenged as ultra vires of the agency’s statutory authority and violative of the Administrative Procedures Act (APA). Below are a few examples of the weaknesses to the FDA’s historical approach to LDT oversight.

First, until 2014, the FDA never attempted formally to articulate the statutory basis for its asserted
jurisdiction over LDTs. In the context of responding to Citizen Petitions challenging the agency’s oversight of LDTs, the FDA engaged in a rather tortured display of exegesis to support its jurisdiction — including the novel proposition that the Federal Food, Drug, and Cosmetic Act (FDCA) does not require “commercial distribution” as a prerequisite to FDA regulation of post-amendment Class III devices. This was a valiant attempt by the agency given the policy position it was seeking to justify, but one whose success in a judicial challenge would have been a tough sell, particularly in light of the reduced deference courts afford agency actions not undertaken through formal rulemaking.[4]

Second, the FDA steadfastly insisted on using guidance documents to effect what would have amounted to a fundamental and profoundly disruptive change to the longstanding regulatory framework governing clinical laboratories. Even for those who support the agency’s view that such significant change to the status quo is necessary to protect the public health, the magnitude of the proposed change demanded notice and comment rulemaking.

Per the FDA’s good guidance practice regulations,[5] guidance documents do not establish legally enforceable rights or responsibilities, and do not legally bind the public or the FDA (although in practice they can exert significant effect). In this instance, the agency’s draft LDT guidance documents purported to impose binding legal requirements on LDTs under which clinical laboratories would have been regulated as device “manufacturers.” The D.C. Circuit has in the past struck down similar attempts by federal agencies to cloak regulation in guidance-document clothing.[6]

Moreover, as the FDA itself acknowledged, existing regulations, in particular those related to the quality system regulations (QSR) for device manufacturers, are not appropriately tailored to clinical laboratory environment, and would have required the agency to issue further guidance adapting the QSR provisions to this context. The unsuitability of existing regulations to a the new context further points to the need for rulemaking to develop regulations informed by the stakeholders who would be required to implement them.

Finally, the FDA’s failure to engage in rulemaking meant that it did not have to systematically address stakeholder concerns in writing, and did not need to analyze or disclose the economic impact of its proposed approach — which the public should be able to evaluate in deciding whether a proposed regulatory action is justified.

Beyond these legal weaknesses, perhaps the biggest challenge to the success of the FDA’s attempts to regulate LDTs has been the agency’s inability to support its core premises that (1) the public health has and will continue to be significantly harmed unless it regulates LDTs, and (2) its existing regulatory framework provides the right set of “tools” (i.e., legal mechanisms) to address these harms.

Despite the FDA’s assertions that “inaccurate or false test results can harm individual patients,” and notwithstanding the LDT Case Study Report it presented Congress,[7] the agency has not presented hard data that LDTs have caused actual harm to patients or that such harms were caused by gaps in LDT oversight — as opposed to inadequate compliance with or enforcement of existing regulatory or professional requirements. If the FDA possesses evidence that patients have been harmed by LDTs, and that such harm resulted from gaps in law or regulation, the agency has a responsibility to share such information with the public.

Separately, if inadequate compliance or enforcement with existing laws and regulations is identified, then certainly those agencies or individuals responsible for such lapses should be held accountable. And, while it is certainly true that absence of evidence of a problem does not mean evidence of absence, the
limited information presented seems a meager foundation to support the far-reaching oversight proposed by the agency.

While only a subset of LDTs would have been subject to premarket review, all clinical laboratories would foreseeably have been responsible for complying with “general” medical device requirements — such as registration and listing, adverse event reporting, recalls and good manufacturing requirements — whose relevance to LDTs is unclear. Surely an incremental approach, targeting discrete and defined harms from specific types of tests, and addressing only those issues not already covered by existing regulatory mechanisms, would have been a more measured response.

To be sure, the LDT Case Study Report did flag some areas where the current system should be improved. For example, doctors and patients would benefit from greater transparency concerning a test’s analytic performance, clinical validation and claims substantiation. But while identifying areas for improvement, the FDA did not convincingly explain why the “tools” contained in its statutory and regulatory toolbox (as opposed to, for example, the tools possessed by the Centers for Medicare and Medicaid Services, the National Institutes of Health, the National Institutes for Standards and Technology or the Federal Trade Commission) would address these concerns, or how its regulatory mechanisms could effectively be adapted to the specific context of clinical laboratory testing.

Some stakeholders no doubt fear that the FDA’s exit (at least temporarily) from center stage presages a “Wild West” scenario. While such a concern is understandable, the FDA’s decision does not leave a complete regulatory “vacuum”; rather other existing federal, state, and private oversight mechanisms continue to govern the activities of clinical laboratories, at least in part.

Furthermore, the FDA will continue to regulate LDTs offered DTC. Finally, the agency retains the “bully pulpit,” which provides a powerful megaphone to denounce specific LDTs that the agency believes pose risk to patients. Indeed, the FDA used this bully pulpit recently when issuing a safety communication warning health care providers and women against the use of Abcodia’s ovarian cancer screening test, effectively halting that company’s planned expansion into the U.S. market. LDT providers seeking to avoid a similar fate should be cautious in their claims and transparent in the scientific support underlying them, and limitations thereto, particularly when offering screening or diagnostic tests for high risk conditions.

Furthermore, the FDA — along with other regulators — can play an important role in monitoring developments in LDTs, identifying novel issues raised by the introduction of new methodologies, convening stakeholders to collaboratively anticipate and respond to developments in the field, and developing consensus-based standards for the development and performance of LDTs.

Thus, while the FDA’s announcement certainly alters the script, it is by no means the end of the story. Clinical laboratories and other stakeholders involved in the development and dissemination of LDTs would be well advised to draft the next chapters carefully. Indeed, reduced government oversight demands greater private sector vigilance and accountability. The success of precision medicine depends on public trust.

Physicians and patients must believe that the tests they use to make significant, life-altering decisions are performed accurately and that the meaning ascribed by clinical laboratories to the test results (i.e., their clinical validity) is supported by sound scientific evidence. The strength of the scientific evidence supporting clinical validity, and any limitations of such evidence, should be clearly disclosed.
New methodologies, in particular next generation sequencing, add additional complexity and require novel expertise, and LDT stakeholders should support the development of standards for performance and use of NGS — and other new technologies that will no doubt emerge — in clinical laboratory testing.

Achieving a truly happy ending to the LDT saga will require that regulators and stakeholders collaborate to achieve the right balance between ensuring patient access to innovative diagnostic technologies and ensuring that the information provided to doctors and patients is analytically and clinically valid and provides actual value in clinical decision making.

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