REGULATORY FOCUS

LDT Regulation: Past, Present and Future

By Jeff Gibbs and Allyson Mullen

This article summarizes the regulatory history of Laboratory Developed Tests (LDTs) and describes where we are now and where we may be heading.

Introduction

George HW Bush was president when the Food and Drug Administration (FDA) first floated the idea that it could regulate Laboratory Developed Tests (LDTs). Four presidents later, the issue of how FDA should regulate LDTs—if at all—remains controversial and unresolved.

The intervening 26 years, though, have hardly been uneventful. There have been lulls and there have been times when it seemed that FDA regulation of LDTs was imminent. At the moment, it seems unlikely FDA will initiate a regulatory regime that covers LDTs. On the other hand, the chances of congressional action seem higher than they have ever been.

Historical Approach to LDT Regulation

In 1976, Congress enacted the *Medical Device Amendments* giving FDA broad authority to regulate medical devices, including *in vitro* diagnostic devices.{1} The statute was silent as to FDA's regulatory authority over clinical laboratories and tests developed and run in those facilities. Congress, subsequently, addressed such laboratories and tests, in 1988, when it enacted the *Clinical Laboratory Improvement Amendments (CLIA)*.{2} This legislation conferred regulatory authority over laboratories and tests run therein upon the Centers for Medicare and Medicaid Services (CMS), not FDA.

FDA first attempted to regulate Laboratory Developed Tests (LDTs)—which were initially called "home brew" tests—in 1992 when FDA was considering how to regulate Research Use Only (RUO) products. In August 1992, FDA released a draft Compliance Policy Guide (CPG) discussing FDA's regulation of RUO products.{3} The draft CPG stated

that "laboratories have been manufacturing 'home brew' products, either from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes" and claimed that "[t]hese products are subject to the same regulatory requirements as any unapproved medical device."{4} FDA's position was challenged in a citizen petition.{5}

While the draft CPG was informal and non-binding, FDA made a more authoritative announcement regarding its authority over LDTs in 1997. This time, FDA issued a regulation creating a class of products called Analyte Specific Reagents (ASRs).{6} In the preamble to the ASR rule, FDA expressly stated that it had regulatory authority over LDTs: "FDA believes that clinical laboratories that develop [LDTs] are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act."{7} However, FDA went on to say that it did not plan to exercise that authority. The preamble stated that while FDA "appreciates the concerns that have been raised about [IVDs] that are not reviewed independently," it believes general controls are sufficient and would only impose additional regulation if "necessary to provide an appropriate level of consumer protection."{8} This began FDA's enforcement discretion policy regarding LDTs.

FDA's next broad LDT policy statement came in 2006, when FDA announced, via a draft guidance document, that it intended to regulate *In Vitro* Diagnostic Multivariate Index Assays (IVDMIAs).{9} In this draft guidance, FDA proposed regulating IVDs that contained complex algorithms.{10} One of FDA's primary concerns was that these "black box" algorithms were not transparent to physicians and could not be readily understood. FDA's policy would have applied to all IVDs, including LDTs that included such algorithms. FDA received significant criticism regarding the IVDMIA draft guidance, including its selective attempt to regulate LDTs using algorithms, and its focus on technology, not risk. FDA never finalized the IVDMIA draft guidance.

FDA, instead, announced it would establish a "risk-based" regulatory framework encompassing all LDTs.{11} As part of its process, in July 2010, FDA held a two-day public meeting to solicit feedback on LDT regulation. The purpose of this meeting was for FDA officials to listen to and understand the laboratory and industry perspective regarding LDT regulation—many of which were heavily critical and skeptical of FDA's attempts. FDA did not reveal its thinking during the meeting.

Four years later, in October 2014, FDA formally released its two draft guidance documents proposing a framework for regulating LDTs, "*FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)*" and "*Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*."{12,13} The draft guidance documents proposed a risk-based system, which would have required the majority of LDTs to be reviewed by FDA over the course of a nine-year phase-in period beginning with the highest risk tests.

In explaining why LDT regulation was necessary, FDA pointed to the changing role of laboratories, both in geographic reach and test complexity.{14] FDA also said that regulation by the agency was needed because of concerns regarding safety of certain LDTs.{15} Pressed by Congress to provide documentation for this claim, FDA released a list of tests that FDA alleged "may have caused or have caused actual harm to patients" due to their failure to comply with FDA requirements related to IVDs.{16} The accuracy of FDA's examples was vigorously contested by laboratories.

Although FDA's proposal was heavily criticized both for its content and for using guidance rather than formal rulemaking, FDA continued to push forward with plans to regulate LDTs. FDA met with key stakeholders and reviewed hundreds of comments on the draft guidances. During this same time, several alternative proposals were floated, including a proposal by the Diagnostic Test Working Group (DTWG) which consisted of both IVD companies and laboratories seeking a balanced approach to LDT regulation. At the same time, other groups began gearing up for potential litigation against FDA.

The 2016 election results, however, ended FDA's most recent plans to regulate LDTs, at least during this administration. On 18 November 2016, FDA notified industry groups and other stakeholders that it would not finalize the two draft guidance documents. FDA stated that it would "continue to work with stakeholders, [the] new administration, and Congress to get [its] approach right."{17,18} And with that declaration, FDA's current attempt to regulate LDTs through policy came to an end, for now.

Current Approach to LDT Regulation

Despite FDA's recent efforts, the 1997 enforcement discretion policy for LDTs remains in effect today. Nonetheless, FDA has sometimes attempted to regulate LDTs indirectly by regulating LDT components, such as sample collection devices, which are considered devices under the *FDC Act.* Collection devices are, for the most part, Class I devices. However, if they are labeled for use with a particular test or for collecting a sample for a particular analyte, the collection device may take on a higher classification and require premarket clearance or approval.

FDA also has taken action against laboratories in other ways, such as "inviting" them to attend meetings, and issuing untitled letters and warning letters, when FDA believes enforcement action is warranted. For example, FDA issued a warning letter to the Laboratory Corporation of America (LabCorp) in 2008 objecting to LabCorp's OvaSure™ test.{19} LabCorp indicated the OvaSure™ test was intended for the detection of early stage ovarian cancer in women with a high risk of developing the disease and had been developed in conjunction with researchers at Yale. FDA concluded Yale had actually developed the test LabCorp was offering, and the OvaSure™ test "is not within the scope of laboratory developed tests over which the [A]gency has traditionally exercised enforcement discretion." In effect, FDA concluded this test was not an LDT.

In another example, FDA sent a warning letter to EXACT Sciences Corporation (EXACT) in 2007 in response to an inspection of a LabCorp facility.{20} LabCorp was offering the PreGen-Plus assay for colorectal cancer screening. FDA concluded the test was not an LDT and required premarket approval, because the assay was designed, developed, validated and marketed by EXACT (not LabCorp). FDA also stated that "equipment and reagents that are required for the test are specified by EXACT (and, in some cases, provided by EXACT)." Ultimately, EXACT obtained premarket approval of the assay.

FDA also may not exercise enforcement discretion with respect to direct-to-consumer (DTC) tests. In November 2013, FDA sent a widely-publicized warning letter to 23andMe, Inc. (23andMe), a DTC genetic testing laboratory, in which it stated that 23andMe was marketing its saliva collection kit and personal genome service without marketing clearance or approval in violation of the FDC Act.{21} Since the 23andMe letter, FDA has issued a number of other untitled and warning letters to laboratories offering DTC LDTs, particularly those offering genetic tests.{22,23} Because some of the tests were ordered by doctors, it has raised the question of what is a DTC test. It appears to be FDA's policy that the ordering physician must be independent of the laboratory.

These examples and others have led to a narrowing of LDTs that are the subject of FDA's enforcement discretion. FDA has said it can regulate LDTs developed by one lab, but performed in another, as well as DTC tests. Some tests that receive specialized equipment, reagents or sample collection devices have been subject to FDA regulation. For example, FDA issued an untitled letter to Matrix Genomics, Inc. citing its distribution of "a home-use buccal swab collection kit" for its Matrix Genomics Breast Cancer Panel without having obtained clearance or approval for the collection kit or panel.{24}

Even for tests that fit the LDT definition, FDA is taking action against categories of tests that it believes present a health risk to patients by issuing safety alerts to patients and healthcare providers. For example, in September 2016, FDA issued two safety communications to women and healthcare practitioners recommending against use of tests that claim to screen for ovarian cancer.{25,26} The communications stated, "there are currently no screening tests for ovarian cancer that are sensitive enough to reliably screen for ovarian cancer without a high number of inaccurate results."

More recently, in November 2018, FDA issued a notice regarding pharmacogenomic tests that could be used to alter drug regimens.{27} FDA asserted these tests were not supported by adequate data. Using unusually bold language, FDA alluded to the possibility of enforcement action: "The FDA is looking into certain developers that may be inappropriately selling genetic tests for the unapproved uses noted above, and will take compliance actions when appropriate." If FDA were to take strong enforcement action against a laboratory and that laboratory chose to contest FDA's action, that could set the stage for a judicial battle over FDA's power to regulate LDTs.

Possible Future Changes to LDT Regulation

Since FDA abandoned its draft LDT guidances in 2016, the potential for future LDT regulation largely lies in the hands of Congress. Many IVD companies and larger laboratories are in support of a legislative approach to regulating LDTs, although no single proposal has yet moved beyond the discussion phase.

For example, in March 2017, Representatives Larry Bucshon (R-IN) and Diana DeGette (D-CO) released a bi-partisan discussion draft of the *Diagnostic Accuracy and Innovation Act (DAIA).{28}* The DAIA would update the regulatory framework to specifically address diagnostic tests and create three distinct areas of activity:

1. test development and manufacturing, which would be regulated by FDA and require premarket review of most tests
2. laboratory operations, which would continue to be regulated by CMS under CLIA
3. medical use/interpretation by a healthcare professional, which would continue to be addressed by state law

The DAIA required regulations to be issued within three years of enactment followed by at least a two-year period for laboratories to come into compliance.

In August 2018, FDA provided Technical Assistance (TA) to the draft DAIA in the form of a complete rewrite. Much like the draft LDT guidance documents, FDA's TA takes a risk-based approach to regulating LDTs. Instead of three levels of risk (low, moderate, and high), FDA's TA adopts a two-tiered approach and allows for pre-certifying of certain tests to avoid FDA premarket review. The concepts in both the DAIA and FDA's TA appear to have been well received by many, but they also both leave specifics to be resolved. The major complaints against FDA's TA include the lack of details{29} and need for clarity. The draft legislation raises many questions, including for example how the pre-certification process will work, how general purpose instrumentation will be regulated, and so on. The details will be essential in understanding the scope and applicability of any new law, including the DAIA or FDA's TA.

Due to the limited time in this Congress, it is unlikely that any legislation will be passed in the near term. However, it is possible that legislation could advance in a new Congress next year. The impact of the changes in Congress on the process are currently unknown.

Conclusion

Since 1992, when FDA first asserted the authority to regulate LDTs, the role of LDTs in healthcare has grown increasingly significant. FDA is surely correct in saying that LDTs are more important clinically than they were 26 years ago, and that the nature of LDTs has evolved dramatically as well. However, recognizing this greater significance does not necessarily mean that FDA should regulate LDTs, let alone provide guidance as to what form that regulation should take.

If FDA is going to regulate LDTs, then the authority should be conferred by Congress. That action would remove all doubts over FDA's authority, and provide an opportunity to create a regulatory structure that actually is suitable for modern LDTs. And, unlike any attempt by FDA to regulate by policy, it would be largely immune from litigation. Whether Congress will go ahead and enact the necessary legislation, though, remains to be seen. If it doesn't, we can expect the question of whether LDTs should be regulated by FDA to surface during the terms of future presidents.

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About the Authors

Jeffrey N. Gibbs, JD, is a director at Hyman, Phelps & McNamara, P.C., Washington, DC, specializing in FDA regulation of devices and diagnostics. He has written and spoken extensively on these topics. He was previously an associate chief counsel for Enforcement at FDA. He currently serves as chairman of the Food and Drug Law Institute. He can be reached at jgibbs@hpm.com.

Allyson B. Mullen, JD, is a director at Hyman, Phelps & McNamara, P.C., Washington, DC, specializing in FDA regulation of devices and diagnostics. She counsels medical device and *in vitro* diagnostic manufacturers on pre and postmarket regulatory matters. She was previously in-house counsel at an in vitro diagnostic device company. She can be reached at amullen@hpm.com.

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