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FDA Regulation of Laboratory-Developed Tests (LDTs)

Laboratory-developed tests (LDTs) are a class of in vitro diagnostic (IVD) device that is designed, manufactured, and used within a single laboratory. LDTs may be used in the context of identifying evolving diseases (e.g., new strains of infectious disease) or those subject to advancing scientific research (e.g., genomic cancer testing). LDTs increasingly incorporate complex technology (e.g., artificial intelligence [AI] software applications) and guide critical health care decisions. Experience with development of tests during the COVID-19 pandemic demonstrated the pivotal role LDTs play in facilitating rapid access to tests, and at the same time highlighted challenges with their regulation.

The regulation of LDTs has been the subject of ongoing debate in recent decades, driven in large part by the increase in the number and complexity of these tests. In general, the Food and Drug Administration (FDA) has maintained that it has clear regulatory authority over LDTs, as it does with all IVDs that meet the definition of *device* in the Federal, Food, Drug, and Cosmetic Act (FFDCA). FDA regulates the safety, effectiveness, and quality of the design and manufacture of IVDs pursuant to authority in the FFDCA. However, FDA traditionally exercised enforcement discretion over LDTs—choosing not to enforce applicable legal requirements with respect to such tests—meaning that most of these tests have neither undergone premarket review nor received FDA clearance, authorization, or approval for marketing. (For more information about FDA regulation of medical devices, see CRS Report R47374, *FDA Regulation of Medical Devices*.) Some representatives of clinical laboratories and manufacturers of LDTs have asserted that LDTs are clinical services and not medical products, and therefore should be outside of FDA's regulatory purview.

Given the importance and complexity of LDTs, Congress and FDA continue to debate their appropriate regulation. Despite an absence of FDA guidance on broader LDT regulation, the agency has asserted authority over subsets of higher-risk LDTs, for example, direct-to-consumer (DTC) genetic tests that provide information about the risk of developing a disease. Most recently, FDA published a final rule (89 *Federal Register* 37286, May 6, 2024) establishing a schedule for phasing out FDA's traditional enforcement discretion policy for LDTs and clarifying that IVDs are medical devices, including when manufactured by laboratories. This followed an October 2023 proposed rule (see CRS In Focus IF12628, *Regulation of Laboratory-Developed Tests: FDA's Proposed Rule*). The final rule requires compliance with device regulatory controls for most LDTs over a period of four years. Observers note that FDA took this step after Congress did not include authorizing legislation to regulate in vitro clinical tests, including LDTs, in user fee reauthorization in 2022.

History of FDA Oversight: 2006-2021

FDA traditionally focused its enforcement on commercial IVDs (test kits) and has not generally enforced premarket or other regulatory requirements for LDTs. Over the past two decades, FDA indicated its intent to regulate LDTs using a risk-based approach due to their increasing number, significance, and complexity. In 2006 and 2007, FDA published and updated draft guidance on a subset of LDTs called In Vitro Diagnostic Multivariate Index Assays (IVDMIAs). IVDMIAs were defined by the FDA as tests that, among other things, provide results that are not transparent and that the end user (usually a physician) could not independently derive. FDA never finalized this guidance and instead announced its intent to regulate all LDTs in a July 2010 public meeting, "Oversight of Laboratory Developed Tests."

October 2014 Draft Guidance

In July 2014, FDA notified Congress of its intent to begin regulating LDTs through draft guidance. The notification complies with a statutory requirement in the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA, P.L. 112-144) that directed FDA to notify Congress at least 60 days before issuing any draft or final guidance on regulation of LDTs. In the October 2014 draft guidance, *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*, FDA presented the details of a risk-based framework for regulating LDTs. The framework generally identified classes of LDTs that would be (1) exempt from regulation entirely; (2) required to meet only registration and listing (or notification) and adverse event reporting requirements; or (3) required to meet registration and listing (or notification), adverse event reporting, applicable premarket review, and quality system regulation requirements. The determination to continue enforcement discretion—or to enforce certain or all applicable regulatory requirements—for an LDT would be based on risk evaluation. FDA collected comments on the draft guidance; however, in November 2016, the agency announced it would be delaying finalization.

January 2017 Discussion Paper

FDA summarized the comments it received on the 2014 draft guidance in a January 2017 *Discussion Paper on Laboratory Developed Tests (LDTs)*, noting that it would not be issuing "a final guidance on the oversight of [LDTs] at the request of various stakeholders to allow for further public discussion … and to give our congressional authorizing committees the opportunity to develop a legislative solution." The discussion paper included a proposed framework for LDT oversight that would focus on "new and significantly modified high and moderate risk LDTs." Previously marketed LDTs would be grandfathered and would not be expected to comply with most or all FDA

regulatory requirements, such as premarket review, unless necessary to protect the public health. In addition, new and significantly modified LDTs in several specified categories (e.g., LDTs for rare diseases) would generally not be expected to comply with FDA regulatory requirements.

COVID-19 Pandemic

The COVID-19 pandemic highlighted issues with LDT regulation, specifically how the enforcement discretion policy interacted with a public health emergency and its related requirements. Many LDT developers, for example, did not recognize that COVID-19 LDTs had to have an Emergency Use Authorization (EUA) prior to marketing or clinical use. This requirement was unfamiliar to many LDT developers, and in an effort to facilitate access to testing, FDA developed a COVID-19 test policy allowing certain laboratories to use their LDTs after notification to the agency but prior to FDA granting an EUA for the test. Subsequently, FDA reported that this modification, in combination with the EUA's lesser evidentiary standard, resulted in the use of LDTs that "proved to have performance problems or to be poorly validated."

FDA's LDT Final Rule (May 2024)

The LDT final rule adopts a single amendment to the existing regulatory definition for *in vitro diagnostic products* to clarify that IVDs, where the manufacturer is a clinical laboratory, meet the definition of *device* under the FFDCA (21 C.F.R. §809.3). The amended definition is as follows (change italicized):

> In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act, *including when the manufacturer of these products is a laboratory*.

In addition, the final rule outlines a *phaseout policy* for FDA's general enforcement discretion approach for LDTs. Specifically, the final rule requires compliance with device regulatory controls (e.g., adverse event reporting, labeling, premarket notification) to be phased in over a period of approximately four years with respect to IVDs manufactured and offered as LDTs. The timing of the cascading phaseout policy is based on time from publication of the final rule (May 6, 2024). In addition to addressing FDA's stated public health concerns with LDTs, the phasing out of FDA's enforcement discretion approach is viewed as a way to level-set regulation of LDTs and traditional commercial IVDs. The different regulatory approach has been highlighted as a concern by IVD manufacturers and related stakeholders. The phaseout policy includes five stages, as follows:

1. One year after publication of the final rule (May 6, 2025): Manufacturers of IVDs offered as LDTs must comply with medical device adverse event reporting (MDR, 21 C.F.R. Part 806) and reports of corrections and removals (21 C.F.R. Part 803). This allows FDA to begin monitoring the safety of LDTs as soon as practically possible. In addition, manufacturers must comply with quality system (QS) requirements regarding complaint files (21 C.F.R. §820.198).

2. Two years after publication of the final rule (May 6, 2026): In addition to the above requirements, manufacturers of IVDs offered as LDTs are required to comply with additional regulatory controls *other than* the QS regulation (device current good manufacturing practices) and premarket review requirements (e.g., Premarket Approval [PMA]). These additional controls include labeling (both general and IVD-specific; 21 C.F.R. Parts 801 and 809), registration and listing (21 C.F.R. Part 807 other than Subpart E), and investigational device requirements (21 C.F.R. Part 812).

3. Three years after publication of the final rule (May 6, 2027): Manufacturers of IVDs offered as LDTs must comply with the QS regulation (21 C.F.R. Part 820), except those IVDs for which all manufacturing activities occur within a single clinical laboratory and the IVD is not distributed outside that laboratory, which must comply with a subset of requirements, including design controls (21 C.F.R. §820.30), records requirements (21 C.F.R. Part 820, Subpart M), and purchasing controls (21 C.F.R. §820.50).

4. Three and a half years after publication of the final rule (November 6, 2027): Manufacturers are required to comply with premarket review requirements for high-risk (Class III) IVDs offered as LDTs (PMA, 21 C.F.R. Part 814). This includes those IVDs that are subject to licensure requirements under PHSA Section 351. In cases where a submission has been received by FDA at the beginning of this stage, the agency will exercise enforcement discretion during the pendency of review.

5. Four years after publication of the final rule (May 6, 2028): Manufacturers must comply with premarket review requirements for moderate- and low-risk IVDs offered as LDTs (21 C.F.R. Part 807, Subpart E, premarket notification; 21 C.F.R. Part 860, Subpart D, De Novo classification request). In cases where a submission has been received by FDA at the beginning of this stage, the agency will exercise enforcement discretion during the pendency of review.

The final rule's applicability is complex. Certain categories of LDTs are currently already subject to all regulatory requirements and are therefore outside the scope of the phaseout policy (e.g., tests developed for emergencies under FFDCA Section 564, direct-to-consumer tests). Certain categories will remain under a policy of complete enforcement discretion (e.g., 1976-type LDTs, forensic tests, LDTs manufactured and performed within DOD or VHA) or partial enforcement discretion (e.g., will not be required to comply with premarket review and/or most QS regulation requirements).

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