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Regulation of Laboratory-Developed Tests: FDA's Proposed Rule

The Food and Drug Administration (FDA) defines laboratory-developed tests (LDTs) as a class of in vitro diagnostic (IVD) device that is designed, manufactured, and used within a single clinical laboratory. LDTs are an important part of personalized medicine and are often modified iteratively, as they test for disease in the context of evolving scientific knowledge (e.g., genomic testing for cancer). LDTs increasingly rely on complex technology (e.g., artificial intelligence [AI] software applications) and guide critical health care decisions.

These considerations, most recently highlighted by COVID-19 test development and deployment during the pandemic, have driven debate over the regulation of LDTs for more than three decades. In general, 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). However, FDA has traditionally exercised enforcement discretion over LDTs—choosing not to enforce applicable statutory and regulatory 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. To date, FDA has focused its oversight on IVD test kits or components, which are commercially marketed as opposed to developed and carried out in a single laboratory. Some representatives of clinical laboratories and manufacturers of LDTs, such as the American Clinical Laboratory Association (ACLA), have long asserted that LDTs are professional clinical services and not medical products, and therefore should fall outside FDA's regulatory purview.

Relevant Congressional and FDA Activity

Given the growing use and complexity of LDTs, as well as experience gained during the COVID-19 pandemic, both Congress and FDA have again focused on the regulation of LDTs. Since passage of the 21st Century Cures Act (P.L. 114-255) in late 2016, various legislative approaches to the regulation of IVDs and LDTs have been considered. The Verifying Accurate, Leading-edge, IVCT Development (VALID) Act, the culmination of many of these earlier efforts, was first introduced in the 116th Congress (S. 3404/H.R. 6102) and again in the 117th (S. 2209/H.R. 4128) and 118th (H.R. 2369). The VALID Act proposes a comprehensive, novel, risk-based regulatory regime for "in vitro clinical tests (IVCTs)," defined to include both IVDs and LDTs, that is distinct from, although similar to, the existing regulatory regime for medical devices. The VALID Act proposes a unique marketing pathway for moderate risk IVCTs predicated on a technology certification covering similar tests marketed by a specific test developer, among many other requirements. In 2022, it was incorporated into an FDA user fee reauthorization bill in the Senate (S. 4348, Subtitle C—In Vitro Clinical Tests); it was not ultimately included in the enacted user fee reauthorization law (neither in the user fee program reauthorization nor in the package of policy riders that passed separately as part of the 2023 omnibus).

In the absence of congressional action, in October 2023, FDA published a proposed rule (88 Fed. Reg. 68006, October 3, 2023) to "make explicit that IVDs are devices under the Federal Food, Drug, and Cosmetic Act, including when the manufacturer of the IVD is a laboratory." In addition, in August 2020 the Department of Health and Human Services (HHS) announced that, during the height of the COVID-19 pandemic, it was rescinding all guidance, compliance manuals, website statements, or other informal issuances concerning FDA premarket review of LDTs. This announcement applied to all LDTs—including COVID-19 LDTs—and stated that FDA could not require premarket review for these tests absent a notice-and-comment rulemaking process. Although this policy was eventually rescinded in November 2021, it highlighted potential challenges for the agency proceeding with oversight of LDTs through agency level guidance rather than formal rulemaking. FDA received nearly 7,000 comments on the proposed rule during a 60-day comment period (which the agency declined to extend); the final rule is currently anticipated in mid-2024.

Overview of Proposed Rule

The proposed rule would make 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 proposed amended definition is as follows (proposed 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) 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 proposed rule outlines a "phaseout policy" for FDA's general enforcement discretion approach for LDTs. Specifically, the rule notes that compliance with device regulatory controls (e.g., adverse event reporting,

labeling, premarket notification) would be phased in over a period of approximately four years with respect to tests manufactured and offered as LDTs. The timing of the cascading phaseout policy is based on time from publication of a final rule. In addition to addressing FDA's stated public health concerns with LDTs, the phasing out of FDA's current general enforcement discretion approach was proposed by FDA to level-set the regulation of LDTs and traditional commercial IVDs. The current differential regulatory approach has regularly been highlighted as a concern by IVD manufacturers and their advocacy organization, AdvaMed. The proposed phaseout policy would include five steps, as follows:

1. *One year after publication of the final rule:* Manufacturers of IVDs offered as LDTs would be expected to 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 would allow FDA to begin monitoring the safety of LDTs as soon as practically possible.
2. *Two years after publication of the final rule:* In addition to MDR and removal and correction notification requirements, manufacturers of IVDs offered as LDTs would be required to comply with additional regulatory controls *other than* Quality System (QS) regulation (device current good manufacturing practices) and premarket review requirements (e.g., Premarket Approval [PMA]). These additional controls include labeling (21 C.F.R. Part 801 and 809), registration and listing (21 C.F.R. Part 807 other than Subpart E), and investigational use requirements (21 C.F.R. Part 812).
3. *Three years after publication of the final rule:* Manufacturers of IVDs offered as LDTs would be required to comply with the QS regulation (21 C.F.R. Part 820), except for IVDs where all manufacturing activities occur within a single clinical laboratory and the IVD is not distributed outside that laboratory. In this case, laboratories would have to comply only with certain QS requirements, for example, 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), among others.
4. *Three and a half years after publication of the final rule* (*but not before October 1, 2027):* Manufacturers would be required to comply with premarket review requirements for high-risk (Class III) IVDs offered as LDTs (PMA, 21 C.F.R. Part 814).
5. *Four years after publication of the final rule (but not before April 1, 2028):* Manufacturers would be required to 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).

FDA notes that its policy of enforcement discretion would continue with respect to certain categories of LDTs, specifically (1) LDTs used for law enforcement purposes (forensic tests); (2) human leukocyte antigen (HLA) LDTs; (3) public health surveillance tests; and (4) "1976-Type LDTs" (tests with characteristics similar to LDTs offered in 1976, for example, use of manual techniques). FDA also notes that certain subsets of LDTs are currently, and generally have been, excluded from the policy of enforcement discretion, and that would continue unchanged. These categories include (1) tests used under an Emergency Use Authorization (EUA); (2) direct-to-consumer tests; and (3) tests intended as blood donor screening or human cells, tissues, and cellular and tissue-based products (HCT/Ps) donor screening tests required for infectious disease testing.

Selected Policy Considerations

On March 21, 2024, the House Energy and Commerce Committee's Subcommittee on Health held a hearing, "Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule." Several witnesses and Members addressed considerations around regulating LDTs through rulemaking or legislative action and provided a range of feedback on FDA's proposed rule. Further, on March 13, 2024, the ranking member of the Senate Health, Education, Labor and Pensions (HELP) Committee formally requested stakeholder feedback on the regulation of clinical tests broadly, prompted in part by FDA's proposed rule.

Policy considerations raised by the proposed rule may include, among others, the following:

- Does FDA need additional statutory authority to regulate LDTs as devices?
- Is the existing medical device regulatory framework sufficiently flexible for the purpose of regulating LDTs?
- How would the FDA's proposed rule interact with Clinical Laboratory Improvement Amendments of 1988 (CLIA) requirements for clinical laboratories?
- FDA estimates there are about 80,000 LDTs currently available, with approximately 8,000 new tests expected per year. Could premarket review of LDTs be adequately managed by FDA and third-party reviewers?
- Would premarket review and other regulatory control requirements affect the availability of LDTs? If so, to what extent?

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