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Potential Broader Effects Of FDA's Lab-Developed Test Rule

By **Lisa Dwyer, Jeffrey Shapiro and Elaine Tseng** (October 16, 2023, 12:57 PM EDT)


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On Sept. 29, the U.S. Food and Drug Administration published the long-awaited proposed rule on laboratory-developed tests.

Unsurprisingly, the proposed rule shows that the FDA has not significantly changed its thinking on laboratory-developed tests in the last decade — since 2014, when the agency issued draft guidance on the topic. In reading through the preamble to the LDT proposed rule, we could not help feeling a sense of déjà vu:

- The FDA is still asserting that it has statutory authority over all LDTs, which are in the FDA's view, a type of in vitro diagnostic test, or IVD;
- The preamble to the proposed rule contains an enforcement discretion policy — similar to that articulated in the 2014 LDT draft guidance — that proposes to phase in the active regulation of LDTs as "devices," using a risk-based approach;
- The FDA's rationale for asserting jurisdiction over LDTs has not changed, although the agency has spent the last nine years bolstering its list of examples to support its argument that greater oversight of LDTs will better protect the American public; and
- The FDA's very narrow informal definition of LDT, which previously has been a lightning rod, has not changed. The FDA is still defining an LDT as "an IVD that is intended for clinical use and that is designed, manufactured, and used within a single [Clinical Laboratory Improvement Amendments of 1988]-certified laboratory that meets the regulatory requirements under the CLIA to perform high complexity testing."

The only proposed change to the codified regulation is to revise the FDA's definition of "in vitro diagnostic products" at Title 21 of the Code of Federal Regulations, Section 809.3, to expressly include in vitro diagnostic products "when the manufacturer of these products is a laboratory."

The practical effect of the LDT proposed rule, for now, is that it may help obtain a tactical advantage in the LDT wars.

Traditionally, battle lines have been established between (1) those who believe that the FDA needs to exert more oversight over LDTs, and (2) those who believe that the CLIA, which regulates laboratories, already provides sufficient oversight of LDTs and that additional FDA oversight would slow or even prevent important innovations from emerging.

The FDA's first salvo to more actively regulate LDTs, the 2014 LDT draft guidance, proved to be so controversial that the guidance was never finalized and many on both sides of the battle lines began to push for legislation that would create a more level playing field between LDTs and other IVDs, without hindering innovation.

That effort ultimately led to proposed legislation, the Verifying Accurate, Leading-edge IVCT Development Act. When VALID failed to pass last year in the December omnibus spending bill, the fight shifted back to the agency.

If past is prologue, the FDA's LDT proposed rule, like the 2014 LDT draft guidance, will spark enough controversy to shift the battle back to Congress. This is especially true given that the estimated price tag of the rule is in the range of $5.5 bllion per year. Moreover, if the proposed rule is finalized, the new frontier in the war will be in the courts.

To us, it seems that the practical intent of this proposed rule is to raise the price Congress will pay for continued failure to pass legislation. The FDA has effectively said it will regulate if Congress does not legislate.

This move will increase the pressure on Congress to adopt legislation. Below, we provide: (1) additional background regarding the genesis of the LDT proposed rule, (2) a summary of the proposed rule and the adjacent enforcement discretion policy, and (3) practical takeaways.

Genesis of the LDT Proposed Rule

The FDA, in issuing the LDT proposed rule, provides a history lesson regarding its oversight of LDTs — and that history lesson is almost identical to the one the FDA provided in the 2014 LDT draft guidance.

According to the FDA, in 1976, the Food, Drug and Cosmetic Act was amended to create a comprehensive system for the regulation of medical devices, and at that time, the definition of a "device" was amended to explicitly encompass IVDs.

The FDCA defines the term "device" in pertinent part as "an instrument, apparatus ... in vitro reagent, or other similar or related article, including any component, part, or accessory, which is ... intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.[1]

According to the FDA in the preamble to the proposed rule, a straightforward interpretation of this text is that it covers all IVD test systems — e.g., systems that include "reagents instruments, specimen collection devices, software and other related materials" — and that it applies equally to test systems manufactured in labs and those manufactured by conventional device manufacturers.

That said, the FDA concedes that regardless of its long-standing statutory authority to regulate LDTs, it initially exercised enforcement discretion over, i.e., did not actively regulate, LDTs because they

presented less risk than other IVDs.

According to the FDA, LDTs were lower risk because they were generally used in the context of rare diseases and to meet the needs of local populations; and they were generally well characterized, performed by lab personnel with requisite expertise, and used by single institutions, housing both the patient's physician and the lab responsible for patient care.

In the FDA's view, however, LDTs have evolved significantly since 1976. Many LDTs now rely on complex instrumentation and software to generate results; and "they are often used in laboratories outside of the patient's healthcare setting and often manufactured in high volume for large and diverse populations." As such, the FDA believes that modern LDTs have similar risk profiles as other IVDs.

With that in mind, the FDA has taken steps over the last decade to exert more oversight over LDTs, but those steps have often been met with significant pushback.

As mentioned, in 2014, the FDA issued the 2014 LDT draft guidance, which used a risk-based approach to phase in additional oversight of LDTs. The guidance was controversial because of concerns that it would stymie innovation without countervailing public health benefit.

The pervasive cry from opponents in Congress and others was, "What is the problem that the FDA is trying to solve?" In the end, the 2014 LDT draft guidance was never finalized; it spurred an effort to enact less draconian legislation; and that effort eventually manifested in the introduction of VALID.

The FDA rattled its saber again in 2019, when it issued a now notorious warning letter to Inova Genomics Laboratory, in which it stated that:
FDA has not created a legal "carve-out" for LDTs such that they are not required to comply with the requirements of the Act that otherwise would apply ... Although FDA has generally exercised enforcement discretion for LDTs, the Agency always retains discretion to take action when appropriate, such as when it is appropriate to address significant public health concerns.

The FDA, however, experienced pushback in the midst of a spat during the pandemic between the U.S. Department of Health and Human Services and FDA over whether the FDA could require LDTs for COVID-19 tests to have emergency use authorizations.

The FDA typically actively regulates LDTs used for emergency use. Regardless, in August 2020, the HHS posted a statement on its website providing that "the department has determined that [FDA] will not require premarket review of [LDTs] absent notice-and-comment rulemaking."

Before responding to the HHS' recission statement with a proposed rule — the first step in notice-and-comment rulemaking — the FDA waited for the battle to play out in Congress. When VALID failed to pass last year in the December omnibus spending bill, the war shifted back to the agency, and the agency responded last week with the LDT proposed rule.

One significant difference between the FDA's opening salvo and its latest is that the FDA learned from its past mistakes. The FDA worked hard to document the problem that additional oversight of LDTs would solve.

After noting that it is estimated that "70 percent of medical decisions are based on laboratory test results," the agency provided a long list of examples to suggest that existing oversight of LDTs is

insufficient to ensure their accuracy.

Examples include: (1) the FDA's experience in reviewing LDTs related to COVID-19, where of the first 125 emergency use authorization requests received from labs for molecular diagnostic tests, "82 showed test design or validation problems," (2) a report that a blood-based lung cancer test underestimated cancer risk in about 40% of patients, and (3) a number of reports concerning erroneous cancer, prenatal and infectious disease tests.

Summary of the LDT Proposed Rule and Proposed Enforcement Discretion Policy

As discussed, the only proposed change to the codified regulation is to revise the FDA's definition of "in vitro diagnostic products" at Title 21 of the Code of Federal Regulations, Section 809.3, to expressly include in vitro diagnostic products "when the manufacturer of these products is a laboratory."

Accordingly, the thrust of the FDA's effort last week was to articulate an enforcement discretion policy that proposes to phase in the active regulation of LDTs as "devices," using a risk-based approach. An overview of the FDA's proposed policy follows.

Definition of LDT

As mentioned, the FDA's very narrow definition of LDT, which previously has been a lightning rod, has not changed.

The FDA is still defining "LDT" as "an IVD that is intended for clinical use and that is designed, manufactured, and used within a single CLIA-certified laboratory that meets the regulatory requirements under CLIA to perform high complexity testing."

In the 2014 LDT draft guidance, the FDA made clear that it does not consider IVDs to meet the definition of LDT if, among other things:

- An entity that owns several clinical laboratories develops a device in one of its clinical laboratories and then transfers the device to other clinical laboratories within its network;

- An academic institution develops a test and then allows a private company with a CLIA-certified laboratory to manufacture the test and provide clinical diagnostic results; or

- A laboratory contracts with a third-party manufacturer to produce a key component, e.g., a coated microtiter plate or specialized specimen collection kit, for the test.

Nothing in the LDT proposed rule suggests that the FDA has changed its mind.

Scope of Newly Proposed Enforcement Discretion Policy

The policy would cover all tests that meet the definition of "LDT" above, as well as tests that are offered, as LDTs that do not technically meet the definition of LDT because the FDA recognizes that "not all laboratories have understood" the FDA's definition of LDT.

The policy, however, would not apply to tests that have traditionally been excluded from the FDA's enforcement discretion policy for LDTs, including for example: (1) tests intended for emergencies

declared under Section 564 of the FDCA, Title 21 of the U.S. Code, Section 360bbb-3, and (2) direct-to-consumer.

In addition, the FDA plans to continue its policy of enforcement discretion for:

- 1976-type LDTs, i.e., those that use manual techniques performed by laboratory personnel with specialized expertise, that have components that are legally marketed for clinical use, and that are designed, manufactured and performed in a single CLIA lab that meets the requirements for high-complexity labs;

- Certain types of human leukocyte antigen tests;

- Tests solely intended for forensic use; and

- Tests exclusively used for public health surveillance.

Stages of the Phasing Out of the FDA's Existing Enforcement Discretion Policy for LDTs

- Stage 1: End the general enforcement discretion approach with respect to medical device reporting requirements and correction and removal reporting requirements one year after the FDA publishes a final phase-out policy, which the FDA intends to issue in the preamble of the final rule.

- Stage 2: End the general enforcement discretion approach with respect to registration and listing, labeling requirements, and investigational use requirements, two years after the FDA publishes a final phase-out policy.

- Stage 3: End the general enforcement discretion approach with respect to quality systems requirements three years after the FDA publishes a final phase-out policy.

- Stage 4: End the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs, i.e., IVDs that may be eligible for classification into class III, and are therefore required to submit a premarket approval application, after the FDA publishes a final phase-out policy, but not before Oct. 1, 2027.

- Stage 5: End the general enforcement discretion approach with respect to premarket review requirements for moderate-risk and low-risk IVDs, i.e., those that require Section 510(k) applications or de novo applications, four years after the FDA publishes a final phase-out policy, but not before April 1, 2028.

Key Takeaways

Significantly, the FDA's LDT proposed rule and its proposed enforcement discretion policy are not final, and therefore, they are not yet in effect.

It is unclear, given the controversial history, and the battles that are yet to come, whether they will ever go into effect. The FDA likely knows that its proposed rule is a threatened hammer that may make compromises in Congress related to VALID, or legislation like it, more palatable.

If the LDT proposed rule and the enforcement discretion policy are finalized, it is likely to spur litigation, and the FDA's position in court will be stronger with a regulation in place than without.

In the event that the LDT proposed rule and the proposed enforcement discretion policy do go into effect, it is hard to imagine that the FDA will not be overwhelmed operationally, as soon as premarket submissions are required.

The FDA's handling of the voluminous submissions for emergency use authorizations for COVID-19 tests during the pandemic did not inspire confidence. The agency was widely criticized for delaying the rollout of the tests, and potentially missing an opportunity to prevent widespread transmission of the disease.

The FDA is likely to receive an even greater number of applications with the phasing out of its current enforcement discretion policy.

Once the number of tests is better understood, we would not be surprised if the FDA issues a series of so-called baby guidances that continue the enforcement discretion policy for certain types of tests for longer periods, so that the FDA can effectively titrate the number of premarket review submissions it receives in a given time period.

Meanwhile, in the preamble of the LDT proposed rule, the FDA makes clear that its proposal to phase out its current enforcement discretion policy "does not in any way alter the fact that it is illegal to offer IVDs without complying with applicable requirements." With that in mind, the FDA states that it "retains discretion to pursue enforcement action at any time against violative IVDs when appropriate."

As a practical matter, the LDT proposed rule is a battle cry with far-reaching ramifications for a range of stakeholders, including clinical laboratories, IVD manufacturers, academic medical centers, health care providers and patients.

It will be important for affected parties to carefully consider the implications of the FDA's proposal in the context of their operations and to develop coordinated regulatory, legislative and litigation strategies. Comments on the LDT proposed rule are due on Dec. 2.

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[1] 21 U.S.C. § 321(h)(1) (emphasis added); see also 21 U.S.C. § 360j(o) (exempting certain types of software from the definition of "device").