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Client Alert

FDA and Life Sciences

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FDA's Latest Salvo in the LDT Wars

For more information, contact:

Lisa M. Dwyer
+1 202 626 2393
ldwyer@kslaw.com

Jeffrey Shapiro
+1 202 626 2927
jshapiro@kslaw.com

Elaine H. Tseng
+1 415 318 1240
etseng@kslaw.com

Jessica Ringel
+1 202 626 9259
jringel@kslaw.com

D. Kyle Sampson
+1 202 626 9226
ksampson@kslaw.com

Eva Temkin
+1 202 626 5418
etemkin@kslaw.com

David J. Farber
+1 202 626 4800
dfarber@kslaw.com

Preeya Pinto
+1 202 626 5547
ppinto@kslaw.com

King & Spalding

Washington, D.C.
1700 Pennsylvania Avenue, NW
Suite 900
Washington, D.C. 20006
Tel: +1 202 737 0500

On September 29, 2023, the Food & Drug Administration ("FDA" or the "Agency") published the long-awaited proposed rule on laboratory developed tests ("LDT Proposed Rule"). The proposed rule is open for public comment through December 2, 2023.

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changed its thinking on laboratory developed tests ("LDTs") in the last decade—since 2014, when the Agency issued draft guidance on the topic ("2014 LDT Draft Guidance").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

- FDA is still asserting that it has statutory authority over all LDTs, which are in FDA's view, a type of *in vitro* diagnostic test ("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preamble to the proposed rule contains an enforcement discretion policy — similar to that articulated in the 2014 LDT Draft Guidance — that proposes to phase in the active regulation of LDTs as "devices," using a risk-based approach;
- FDA's rationale for asserting jurisdiction over LDTs has not changed, although the Agency has spent the last 9 years bolstering its list of examples to support its argument that greater oversight of LDTs will better protect the American public; and
- FDA's very narrow informal definition of LDT, which has been a lightning rod in the past, has not changed. 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 CLIA [Clinical Laboratory Improvement Amendments of 1988]-certified laboratory that meets the regulatory requirements under CLIA to perform high complexity testing*."

The *only proposed change* to the codified regulation is to revise FDA's definition of "in vitro diagnostic products" at 21 C.F.R. § 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 FDA needs to exert more oversight over LDTs, and (2) those who believe that CLIA, which regulates laboratories, already provides sufficient oversight of LDTs and that additional FDA oversight would slow or even prevent important innovations from emerging.

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 ("VALID") 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 — 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 Billion per year. Moreover, if the proposed rule is finalized, the battle will expand to 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. 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 take-aways, including implications for coverage and reimbursement.

GENESIS OF THE LDT PROPOSED RULE

FDA, in the preamble to the LDT Proposed Rule, provides a history lesson regarding its oversight of LDTs — and that history lesson is almost identical to the one FDA provided in the 2014 LDT Draft Guidance. According to FDA, in 1976, the Food, Drug and Cosmetic Act ("FDCA") 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." 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"). According to FDA, 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") — and that it applies equally to test systems manufactured in labs and those manufactured by conventional device manufacturers.

That said, FDA concedes that regardless of its belief in 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 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 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, FDA believes that modern LDTs have similar risk profiles as other IVDs.

With that in mind, FDA has taken a number of steps over the last decade or so to exert more oversight over LDTs, but FDA's steps have often been met with significant push-back. As mentioned, in 2014, 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 was from opponents in Congress and others was "what is the problem that 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.

FDA rattled its saber again in 2019, when it issued a now notorious warning letter to Inova Genomics Laboratory, in which it stated "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."

FDA, however, experienced push-back in the midst of a spat during the pandemic between the Department of Health and Human Services ("HHS") and FDA over whether FDA could require LDTs for COVID-19 tests to have Emergency Use Authorizations ("EUAs"). FDA typically actively regulates LDTs used for emergency use. Regardless, in August 2020, 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 HHS' recission statement with a proposed rule — the first step in notice-and-comment rulemaking — 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 FDA's opening salvo (the 2014 Draft LDT Guidance) and its latest (the LDT Proposed Rule), is that FDA learned from its past mistakes. 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) FDA's experience in reviewing LDTs related to COVID-19, where of the first 125 EUA 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 percent of patients, and (3) a number of reports concerning erroneous cancer, prenatal, and infectious disease tests.

SUMMARY OF THE LDT PROPOSED RULE AND ENFORCEMENT DISCRETION POLICY

As discussed, the *only proposed change* to the codified regulation is to revise FDA's definition of "in vitro diagnostic products" at 21 C.F.R. § 809.3 to expressly include *in vitro* diagnostic products "when the manufacturer of these products is a laboratory." Accordingly, the thrust of FDA's effort last week was to articulate an enforcement discretion policy (similar to that in the 2014 LDT Draft Guidance) that proposes to phase in the active regulation of LDTs as "devices," using a risk based approach. An overview of FDA's proposed policy follows.

- Definition of LDT – as mentioned, FDA's very narrow definition of LDT, which has been a lightning rod, has not changed. FDA is still defining LDTs 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." In the 2014 LDT Draft Guidance, FDA made clear that *it does not consider IVDs to meet the definition of LDT if (among other things)*: (1) 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, (2) 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 (3) a laboratory contracts with a third party manufacturer to produce a key component (e.g., coated microtiter plate, specialized specimen collection kit) for the test. Nothing in the LDT Proposed Rule suggests that 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 FDA recognizes that "not all laboratories have understood" FDA's definition of LDT. The policy, however, *would not apply* to tests that have traditionally been excluded from FDA's enforcement discretion policy for LDTs, including for example: (1) tests intended for emergencies declared under section 564 of the FDCA, 21 U.S.C. § 360bbb-3, and (2) direct-to-consumer (DTC tests) (i.e., those intended for consumer use "without meaningful involvement by a licensed healthcare professional"). In addition, FDA plans to continue its policy of enforcement discretion (i.e., of not actively regulating): (1) "1976-Type LDTs" (i.e., those that use manual techniques (without automation) 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), (2) certain types of Human Leukocyte Antigen ("HLA") tests, (3) tests solely intended for forensic use, and (4) tests exclusively used for public health surveillance.
- **Stages of the *Phase-Out* of FDA's Existing Enforcement Discretion Policy for LDTs (Phase-In of Active Regulation)**
  - **Stage 1**: End the general enforcement discretion approach with respect to *Medical Device Reporting ("MDR") requirements* and *correction and removal reporting requirements* 1 year after FDA publishes a final phaseout policy, which 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*, 2 years after FDA publishes a final phaseout policy.
  - **Stage 3**: End the general enforcement discretion approach with respect to *Quality Systems ("QS") requirements* 3 years after FDA publishes a final phaseout 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 pre-market approval application (PMA)), 3.5 years after FDA publishes a final phaseout policy, but not before October 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 510(k) applications or de novo applications), 4 years after FDA publishes a final phaseout policy, but not before April 1, 2028.

KEY TAKE-AWAYS

Significantly, 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. 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 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 FDA will not be overwhelmed operationally, as soon as premarket submissions are required. FDA's handling of the voluminous submissions for EUAs for COVID-19 tests during the pandemic did not inspire confidence. The Agency was widely criticized for delaying the roll-out of the tests, and potentially missing an opportunity to prevent widespread transmission of the disease. FDA is likely to receive an even greater number of applications with the phase-out of its current enforcement discretion policy. Pew Charitable Trusts recently estimated that 3.3 billion IVD tests (both

LDTs and FDA authorized tests) are *run* every year, and it noted that FDA suggested in 2014 that there were approximately 11,000 types of tests that had been developed in labs. *See* The Role of Lab-Developed Tests in the In Vitro Diagnostics Market, Pew Charitable Trusts, Oct. 22, 2021. We cannot know how many tests may be subject to the new rule and the new policy, until registration and listing take effect. Once the number of tests is better understood, we would not be surprised if FDA issues a series of "baby" guidances that continue the enforcement discretion policy for certain types of tests for longer periods, so that 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, 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, 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, healthcare providers, and patients. It will be important for affected parties to carefully consider the implications of FDA's proposal in the context of their operations and to develop coordinated regulatory, legislative, and/or litigation strategies.

Stakeholders should also consider how the LDT Proposed Rule and the proposed enforcement discretion policy may impact Medicare (and commercial payer) reimbursement for LDTs. Payers have historically been reluctant to extend coverage to LDTs. For over a decade, the Centers for Medicare & Medicaid Services ("CMS") has been on record "with concerns about the quality of laboratory developed tests and the validation being performed on these tests." AHRQ Technology Assessment, Quality, Regulation and Clinical Utility of Laboratory developed Molecular Tests (Oct. 6, 2010). Absent FDA approval or clearance for these tests, laboratories have had to demonstrate analytic validity and clinical validity, as well as clinical utility, before Medicare will cover a test. If the LDT Proposed Rule is finalized, establishing coverage for LDTs will become even more difficult, as laboratories may be expected to obtain FDA approval or clearance in order to secure reimbursement, even before the phase-out of FDA's enforcement discretion policy takes effect.

In any event, stakeholders should take advantage of the opportunity to submit comments on the LDT Proposed Rule by December 2, 2023. FDA has solicited comments on a few topics in particular, including (1) whether there are specific public health rationales that would meet the public health needs articulated in the LDT Proposed Rule and support FDA maintaining a policy of general enforcement discretion for premarket and QSR requirements for some or all LDTs that are currently being marketed; (2) whether specific rationales support a longer phaseout period for tests offered as LDTs by smaller laboratories; (3) whether and what unintended consequences to patient populations may result from FDA's proposed phaseout policy; (4) whether academic medical centers have characteristics that merit continuation of general enforcement discretion for tests they provide; and (5) the appropriateness of continuing general enforcement discretion in circumstances where outside programs can be leveraged (such as the New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP) or Veterans Health Administration (VHA) programs).

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King & Spalding LLP regularly counsels on issues related to IVDs and LDTs. Please let us know if you have any questions regarding the LDT Proposed Rule, or if we can be of any assistance preparing comments or in navigating the changing landscape.

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