Are Concessions In FDA's Lab-Developed Tests Rule Enough?

By **Dominick DiSabatino and Audrey Mercer** (May 8, 2024)

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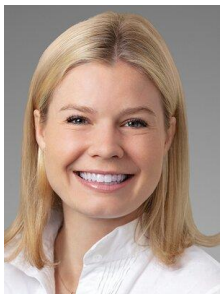

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On April 29, the U.S. Food and Drug Administration issued a highly anticipated — and highly controversial — final rule that rolls out a four-year, five-stage plan that will phase out the agency's previous policy of enforcement discretion for laboratory-developed tests, or LDTs.

The final rule was issued with astonishing speed compared to the FDA's usual rulemaking timeline,[1] coming not even six months after the FDA issued the proposed rule. The urgency with which the FDA turned out the final rule, as well as the rule's whopping 528-page length and the FDA's issuance of three accompanying guidance documents, each underscore LDT regulation as a top priority for the agency.[2]

The FDA has also stated as much, citing patient safety, i.e., ensuring that diagnostics are safe and effective for patient use, as the major impetus for the rule.[3]

However, industry participants have been openly critical of the rule, citing concerns that it will stifle access to and innovation of potentially life-saving diagnostics.[4]

The Final Rule

The final rule makes two pivotal changes, amending the regulatory definition of "in vitro diagnostic products" to include LDTs and phasing out the FDA's previous policy of enforcement discretion for LDTs by implementing a four-year, five-step regulation rollout. It also sets forth some important exceptions, most of which were alluded to, but not formally outlined, in the proposed rule.

The first notable piece of the final rule is a simple, but massive, amendment to the regulatory definition of in vitro diagnostic, or IVD, which adds the following clause to the regulatory definition: "including when the manufacturer of these products is a laboratory."

The FDA has long held the position that all IVDs, including LDTs, are devices under the Federal Food, Drug and Cosmetic Act, but the new rule codifies this interpretation in the form of a more permanent regulation.

Second, the new rule implements a phased approach to ending the FDA's policy of enforcement discretion for LDTs. The phased approach requires LDT sponsors to comply with different FDA device regulations on a staggered timeline, and the clock starts on the final rule's publication date — May 6, the date to which all five stages are anchored.

The five stages are as follows:

1. LDTs are subject to medical device reporting[5] and adverse event reporting[6] one year after the final rule's publication, i.e., May 6, 2025.

2. LDTs are subject to registration/listing,[7] labeling[8] and investigational use[9] requirements two years after the final rule's publication, i.e., May 6, 2026.

3. LDTs are subject to quality system regulations[10] three years after the final rule's publication, i.e., May 6, 2027.

4. High-risk LDTs are subject to premarket review[11] three and a half years after the final rule's publication, i.e., Nov. 6, 2027.

5. Mid- and low-risk LDTs are subject to premarket review[12] four years after the final rule's publication, i.e., May 6, 2028.

In response to the over 6,500 comments received over the proposed rule during the two-month comment period — many of which raised concerns that the sudden regulation of LDTs would limit access to and innovation of critical diagnostics — the FDA's final rule identified eight categories of LDTs for which it will continue to exercise some degree of enforcement discretion.

Most notably, the FDA will grandfather in currently marketed LDTs — i.e., LDTs that were first marketed prior to the final rule — with respect to certain, but not all, regulatory requirements.

Under the final rule, the FDA will require currently marketed LDTs to meet all of the regulatory requirements outlined in the phaseout policy, except for obtaining premarket notification and complying with the quality system regulations, aside from certain recordkeeping and inspection requirements.

Even though this enforcement discretion policy is limited, it is still likely to bring a sigh of relief to the industry at large, since quality system regulations compliance and premarket review come with a significant price tag.

As stated by the FDA, the policy is designed to minimize disruption in the market by exempting LDTs that are currently marketed to patients — and on which patients might currently rely — from some of the more cumbersome regulatory requirements. The policy applies to modifications of currently marketed LDTs as well, subject to certain limitations.

The FDA will also exercise this same scope of enforcement discretion — i.e., with respect only to the premarket review and most of the quality system regulations — for two narrow categories of LDTs designed to test rare conditions and/or fulfill unmet needs:

- Nonmolecular antisera LDTs for rare red blood cell antigens, subject to certain conditions, including the unavailability of a viable alternative; and

- LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

The FDA considers a need to be unmet if:

- There is no FDA-authorized version of the test;

- There is an FDA-authorized test, but either it is not indicated for use for the particular patient or the patient has unique needs; or

- There is an FDA-authorized test but it is not available.

Further, the FDA will exercise varying levels of enforcement discretion for certain LDTs developed and/or reviewed by partnering government agencies. First, the FDA will continue to exercise full enforcement discretion for LDTs manufactured and performed within the Veterans Health Administration or the U.S. Department of Defense, meaning that these LDTs will not be subject to any of the stages of the FDA's phaseout policy.

On the other end of the enforcement discretion spectrum, the FDA will apply its most limited scope of enforcement discretion to LDTs approved by the New York State Clinical Laboratory Evaluation Program in that it will not require these LDTs to undergo premarket review.

Finally, the FDA will continue to exercise full enforcement discretion for the following categories of LDTs, which were included in the framework of the proposed rule: (1) so-called 1976-type LDTs (2) human leukocyte antigen LDTs intended to facilitate transplantation; and (3) forensic use LDTs.

Predictions and Implications

In creating this final rule, the FDA was faced with the near-impossible task of balancing three key interests — patient safety, patient access and diagnostic innovation — a balance it attempts to strike by including a handful of major concessions that were alluded to, but not outlined, in the proposed rule.

In the text of the final rule, the FDA spends over 60 pages justifying the need for increased regulation of LDTs, which, according to the agency, boils down to one key concern — patient safety. More specifically, the FDA points to data exposing a slew of inaccurate LDTs that were marketed to patients during the COVID-19 pandemic, some for serious conditions such as cancer.

Based primarily on this rationale, the proposed rule did receive a number of supportive comments from industry participants. However, of the over 6,500 comments received, far more were penned in opposition to the FDA's proposal. As discussed above, critics claim that the rule presents two high-level threats — limiting patient access and stifling innovation.[13]

The FDA responded by making some major concessions in an apparent attempt to soften the regulatory blow and hedge against the mountain of litigation hurtling its way. From the FDA's perspective, after spending more than a decade crafting a regulatory framework for LDTs, the agency needed to not only usher it through the rulemaking process, but also needed to make every attempt to ensure that the rule, if and when it is challenged, will not be overturned in court.

And although the FDA dismissed the comment that the U.S. Supreme Court's upcoming decision in Loper Bright Enterprises v. Raimondo[14] could undermine the agency's authority to regulate LDTs — and thereby, jeopardize the fate of the new rule — it is still widely anticipated that industry participants will challenge the rule in court.

So, the FDA's concessions — both in the rule and recently stated policy — are strategic.

First, the FDA broadened its original proposal by conceding to grant some level of enforcement discretion for all but one of the categories for which it solicited comments in the proposed rule.[15]

And, second, the FDA announced earlier this year that most Class III devices — which, technically, could include all LDTs — will be reclassified to Class II.[16] It remains to be seen whether this two-pronged approach will be enough to mitigate against the threat of legal challenges from newly regulated entities.

The final rule's policy of continued, albeit limited, enforcement discretion for currently marketed LDTs was drafted largely in response to industry concerns that subjecting these LDTs to regulation would result in a detrimental loss of access to many diagnostics on which patients currently rely. This decision, then, comes as a relief to the burgeoning diagnostics industry, but questions remain about whether and to what extent reclassification will affect material compliance with the phased enforcement rollout.

Further, critics may find the final rule's concessions less generous in terms of fostering diagnostic innovation. The FDA presents several reasons why the final rule does, in fact, foster innovation — including "leveling the playing field" to foster innovation by nonlaboratory manufacturers, saving manufacturers of currently marketed LDTs from having to divert resources from innovation of future LDTs to costs associated with premarket review and quality system regulations compliance, and incentivizing development of LDTs for unmet needs.

But the reality is that future LDTs will be subject to expensive and time-consuming regulatory requirements, which will no doubt hinder at least some of the players on the cutting edge of diagnostic innovation, especially those developing diagnostics for rare diseases that often lack critical funding.

Ultimately, it stands to be seen whether the final rule concedes enough to satisfy the droves of opposing comments issued in response to the proposed rule. After all, industry participants have taken a hardline stance in the past few months, many of which — aside from warning about reduced access and stifled innovation — argue that the FDA doesn't even have the authority to regulate LDTs and advocate for the FDA to wait on a congressionally developed statutory framework.[17]

However, in an election year, and against a long list of national and geopolitical priorities, LDT regulation has largely fallen off the legislative radar.[18] Therefore, critics of the final rule may have to rely on the courts, and we may see a legal challenge, or several, to the final rule later this year.

While industry participants should prepare for compliance with the five stages of the FDA's phaseout policy, they should also keep a close eye on the courts, where, despite the FDA's preemptive efforts, the future of LDT regulation may hang in the balance.

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should not be taken as legal advice.

[1] For example, consider FDA's "intended use" regulations were proposed in 2015 but not made effective until 2021. See 86 Fed. Reg. 41385. https://www.govinfo.gov/content/pkg/FR-2021-08-02/pdf/2021-15980.pdf.

[2] See Draft Guidance (enforcement policy for immediate response tests without a declared emergency) https://www.fda.gov/media/178122/download, Draft Guidance (enforcement policy for testing during a declared emergency) https://www.fda.gov/media/178123/download; LDT FAQs, FDA (Apr. 29, 2024) https://www.fda.gov/medical-devices/laboratory-developed-tests/laboratory-developed-tests-frequently-asked-questions.

[3] See, e.g., Press Release, LDTs, FDA (Apr. 29, 2024) https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests.

[4] See, e.g., Witness Testimony before the Health Subcommittee of the House Energy & Commerce Committee, U.S. House of Representatives (Mar. 21, 2024) https://energycommerce.house.gov/events/health-subcommittee-hearing-evaluating-approaches-to-diagnostic-test-regulation-and-the-impact-of-the-fda-s-proposed-rule.

[5] See21 CFR Part 803.

[6] See21 CFR Part 806.

[7] See21 CFR Part 807.

[8] See21 CFR Parts 801 and 809, Subpart B.

[9] See21 CFR Part 812.

[10] SeeCurrent Good Manufacturing Practices ("CGMP") rules at 21 CFR Part 820.

[11] Seethe Pre-Market Application ("PMA") process at 21 CFR Part 814.

[12] Seethe 510(k) process at 21 CFR Part 807, Subpart E, and/or the de novo request process at 21 CFR Part 860, Subpart D.

[13] See, e.g., supra FN 4.

[14] See Loper Bright Enterprises v. Raimondo, Docket No. 22-451 (on the issue of whether to overturn or significantly limit the Chevron Doctrine) https://www.supremecourt.gov/docket/docketfiles/html/public/22-451.html.

[15] FDA solicited comments on, but did not ultimately extend enforcement discretion to, small laboratories. It is no coincidence, and it was certainly not lost on FDA, that the topic of enforcement discretion for small laboratories received only two (out of over 6,500) comments.

[16] See Press Release, Reclassification Process for Most High Risk IVDs, FDA (Jan. 31, 2024) https://www.fda.gov/medical-devices/medical-devices-news-and-events/cdrh-announces-intent-initiate-reclassification-process-most-high-risk-ivds?utm_medium=email&utm_source=govdelivery.

[17] See id.

[18] For example, Congress has not revisited the issue since the failure of the Verifying Accurate Leading-edge IVCT Development ("VALID") Act in 2022 https://www.congress.gov/117/bills/hr4128/BILLS-117hr4128ih.pdf.