FDA Issues Long-Awaited Proposed Rule To Regulate Laboratory-Developed Tests

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On September 29, 2023, the Food and Drug Administration (FDA) issued a proposed rule that would end its long-standing policy of enforcement discretion with respect to regulation of laboratory-developed tests (LDTs) (the Proposed Rule).[1] Under the Proposed Rule, FDA would add language to the definition of "in vitro diagnostic products" (IVDs) in 21 CFR Part 809.3(a) stating that IVDs are considered devices under the Food, Drug and Cosmetic Act (FDCA), "including when the manufacturer of these products is a laboratory."

Recognizing that treating LDTs as IVDs subject to regulation as medical devices will have profound impacts on clinical laboratories offering LDTs, the Proposed Rule provides for a phased end to FDA's policy of enforcement discretion with respect to LDTs. Under this approach, LDT manufacturers will be required to comply with various medical device regulatory requirements in stages beginning between one and four years after FDA publishes the final LDT rule, the preamble of which will include FDA's final policy regarding this "phaseout" process.

While it is therefore unclear when these regulatory requirements ultimately would become effective, laboratories offering LDTs should be aware of and continue to track developments relating to the Proposed Rule, particularly as it does not propose to "grandfather" any LDTs currently on the market.

Key Points

- FDA proposes to modify the definition of "in vitro diagnostic products" in 21 CFR Part 809.3 to expressly include laboratory-developed tests.
- The change would require all IVDs, including LDTs, to comply fully with FDA's medical device regulatory requirements, including applicable premarket review requirements.
- FDA proposes a phased end to its current policy of enforcement discretion for LDTs, with regulatory requirements becoming applicable in five stages over four years and premarket review requirements falling in the final two stages.
- FDA does not propose to "grandfather" any LDTs on the market but invites comments on the issue.
- Certain specified tests, such as forensic tests and human leukocyte antigen tests, would be excluded from the new enhanced oversight.
- Comments on the Proposed Rule must be submitted by December 4, 2023.

Background on LDT Regulation

FDA regulations define IVDs as "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 and intended for use in the collection, preparation, and examination of specimens taken from the human body."

[1] The Proposed Rule will be published in the Federal Register on October 3, 2023.

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IVDs are medical devices, subject to the full range of premarket and postmarket controls, including requirements pertaining to:

- 510(k) premarket notification or premarket approval (PMA);
- quality system (QS) regulation;
- medical device reporting (MDR);
- registration and listing; and
- labeling.

In addition, IVDs are also generally subject to regulation under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

LDTs are a subset of IVDs that are designed, manufactured and used within a single laboratory (*i.e.*, a clinical lab with a single CLIA certificate). Although FDA historically has maintained that it has the authority to regulate LDTs as medical devices, it generally has not enforced premarket review and other medical device regulatory requirements for LDTs. This policy of enforcement discretion arose because LDTs historically were perceived as low-risk due to their use in limited volumes primarily in rare diseases and generally with interpretation by a treating physician.

However, as FDA describes in the Proposed Rule, over the past 50 years, LDTs have become "used more widely, by a more diverse population, with an increasing reliance on high-tech instrumentation and software, and more frequently for the purpose of guiding critical healthcare decisions." The Proposed Rule therefore asserts that "today's LDTs are similar to other IVDs that have not been [subject to the Agency's] general enforcement discretion approach," such that "phasing out the general enforcement discretion approach for LDTs is important to protect the public health." For purposes of the rule, FDA is defining LDT broadly, asserting that many manufacturers of high complexity tests have cloaked themselves as LDT manufacturers when their tests do not technically qualify as such.

The Proposed Rule is not FDA's first attempt at regulating LDTs. Since at least 2006, both FDA and Congress have repeatedly revisited the approach to regulating LDTs. Congress has never taken action, while FDA has issued draft guidances asserting an intent to require premarket review of LDTs before reconsidering in response to strong pushback. Responses to FDA's proposals questioned whether LDTs are, in fact, subject to FDA jurisdiction, whether additional regulation is appropriate in light of CLIA's application to LDTs and whether additional regulation by FDA would inhibit innovation and restrict patient access.

In 2017, FDA published a white paper proposing enhanced medical device regulatory oversight and invited Congress to take up the issue. The Verifying Accurate, Leading-Edge IVCT Development (VALID) Act has been introduced in the past few Congresses and was expected to be included in the omnibus bill passed at the end of 2022 but ultimately stalled. Against this backdrop, earlier this year, the Biden administration announced that it would undertake LDT rulemaking, leaving industry observers watching closely for the release of the Proposed Rule.

Summary of Proposed Rule

As noted above, the actual changes included in the Proposed Rule are minimal, amounting to the addition of 10 words to the IVD definition, but the potential impacts of this change are significant. In recognition of this impact, and of industry comments received in response to past regulatory attempts, the Proposed Rule provides that FDA will phase out its general enforcement discretion policy with regard to LDTs in five stages over a four-year period:[2]

1. One year after FDA publishes a final phaseout policy in the preamble of the final rule, enforcement discretion would end with respect to both MDR and correction and removal reporting requirements.
2. Two years after publication of the final phaseout policy, enforcement discretion would end with respect to requirements other than MDR, correction and removal reporting, QS, and premarket review. At this stage, LDTs would be required to comply with FDA requirements relating to registration and listing, labeling, and investigational device exemptions.
3. Three years after publication of the final phaseout policy, enforcement discretion would end as to QS requirements (good manufacturing practice requirements applicable to medical devices).
4. Three and a half years after publication of the final phaseout policy (but not before October 1, 2027), enforcement discretion would end with respect to premarket review requirements for high-risk IVDs. At this point, Class III LDTs would be subject to full PMA requirements under the FDCA.

[2] FDA proposes to apply this "phaseout policy to IVDs that are manufactured and offered as LDTs by laboratories that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing, even if those IVDs do not fall within FDA's traditional understanding of an LDT because they are not designed, manufactured, and used within a single laboratory."

5. Finally, four years after publication of a final phaseout policy (but not before April 1, 2028), enforcement discretion would end with respect to premarket review requirements for moderate-risk and low-risk IVDs that require premarket review under applicable regulations. At this point, Class II LDTs (and those Class I LDTs requiring premarket review) would be subject to the full 510(k) premarket notification and *de novo* requirements under the FDCA. The Proposed Rule states that FDA generally would not intend to enforce against LDTs for which 510(k)s and *de novo* applications are submitted in the four-year time frame until FDA's review of the submission is completed.

FDA asserts in the Proposed Rule that "the phaseout of FDA's general enforcement discretion approach for LDTs is intended to help assure the safety and effectiveness of LDTs, and may also foster the manufacturing of innovative IVDs for which FDA has determined there is a reasonable assurance of safety and effectiveness."

Of particular note, the Proposed Rule's current approach of not "grandfathering" LDTs on the market at the time of the final rule is in contrast to the VALID Act and prior proposals by FDA, all of which have included grandfathering provisions. Such provisions are intended to preserve patient access and mitigate economic impact by allowing already marketed LDTs to remain on the market, subject to certain conditions, without the need for subsequent premarket review.

The Proposed Rule does identify certain classes of LDTs, such as forensic tests and human leukocyte antigen tests, that would expressly be exempted from the Proposed Rule's enhanced requirements. But all other LDTs on the market at the time of the final rule would be expected to come into compliance. FDA acknowledges that, under this approach, LDTs on the market may have to come off, but it estimates that nearly 50% of the LDTs on the market today would qualify as low-risk tests that, as Class I devices, would generally not be subject to premarket review even under the new regime.

The Proposed Rule asserts that FDA retains the right to take legal action against any LDT during the final phaseout period should such action be necessary, as well as to promulgate different policies of enforcement discretion for specific LDTs in the future if there is a public health need, as in the case of COVID-19. Finally, the Proposed Rule suggests that FDA may seek to outsource review of the IVD submissions, at least in part, through FDA's Third Party review program to help improve efficiencies.

Impacts of Proposed Rule

With the repeated reintroduction of the VALID Act in recent years and the Biden administration's announcement this year of its intent to begin rulemaking, it has appeared all but certain that LDTs would become subject to greater regulation in the near future. If enacted as proposed, the Proposed Rule will have a profound impact on clinical labs that offer LDTs.

In the near term, clinical labs offering LDTs should consider beginning to develop systems to ensure that they can comply with MDR reporting requirements whenever the first phase of enforcement discretion ends.

Over the years to follow, in order to support premarket review, labs would have to develop evidence of both LDTs' (1) analytical validity (which is currently subject to review under CLIA); and (2) clinical validity (*i.e.*, the accuracy with which an LDT identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient).

Approaches to complying with all of these regulatory requirements, including developing the evidence required to support premarket review, are fairly well established and understood in light of FDA's historical regulation of other IVDs. Nevertheless, the volume of tests that would have to undergo new regulatory scrutiny, and the desire by some to preserve access to LDTs already in the marketplace, will likely result in calls for clarity and reform of clinical expectations.

We also expect judicial challenges to the final rule, as those most opposed to FDA's proposed oversight of LDTs question FDA's jurisdiction to regulate LDTs and may take issue with FDA's assertion of this jurisdiction through rulemaking rather than in response to legislation. To the extent such litigation ensues, it could significantly delay FDA's publication of a final rule and when the rule actually becomes effective.

Clinical laboratories and other stakeholders seeking to comment on the Proposed Rule must do so by the December 4, 2023, deadline.