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Questions Linger After FDA's Lab-Developed Tests Proposal

By **Scott Danzis, Amy Leiser and Wade Ackerman** (October 20, 2023, 5:33 PM EDT)

On Sept. 29, and as widely anticipated, the U.S. Food and Drug Administration announced the publication of a proposed rule to clarify that lab-developed tests, or LDTs, are medical devices subject to FDA regulation.


Scott Danzis

LDTs are diagnostic tests that are developed and offered by high-complexity laboratories certified under the Clinical Laboratory Improvement Amendments.

While the FDA has asserted that it has authority to regulate LDTs as medical devices, it has never broadly exercised that authority. In the proposed rule, FDA seeks to amend its regulation defining in vitro diagnostic products, or IVDs, to add the words "including when the manufacturer of these products is a laboratory."


Amy Leiser

While the proposed new regulatory text is only 10 words, the majority of the regulatory preamble is focused on the FDA's justification for issuing the proposed rule and its claimed legal basis for doing so.

This article does not address the FDA's claimed policy justifications — including its characterization of allegedly problematic LDTs — or the FDA's legal authority to issue the rule. Both topics are highly controversial and will undoubtedly be contested by stakeholders.

Instead, this article is focused on the substance of the proposed policy — a five-stage phase-out of FDA's enforcement discretion policy for LDTs over four years. As described below, the details are slim, and many questions remain unanswered.


Wade Ackerman

Brief Background: History of LDT Regulation

The FDA has asserted that LDTs qualify as medical devices, but the agency has not actively regulated such tests or resolved significant questions about its authority to do so.

This means that the agency has not attempted to require compliance with the Federal Food, Drug and Cosmetic Act, with the exception of certain test categories, such as direct-to-consumer tests, some pharmacogenomic tests and tests that respond to public health emergencies.

Meanwhile, many in the laboratory community and others have long taken the position that the FDA does not have authority under the FDCA to regulate LDTs.

At the same time, over the past several years, Congress has worked with key stakeholders on legislative proposals for regulating diagnostics, including LDTs.

Most notable among these proposals was the Verifying Accurate Leading-edge IVCT Development Act, which was introduced in both the U.S. House of Representatives and U.S. Senate, closely negotiated for months and nearly passed at the end of 2022 in the Consolidated Appropriations Act. Ultimately, the bill was not enacted, and in the spring of this year, the FDA announced its intention to initiate rulemaking for LDTs.

Discussion

As noted above, the text of the proposed rule is short: 10 words asserting that IVDs include products manufactured by a laboratory. The stages for the proposed phase-out of the FDA's decadeslong enforcement discretion policy is summarized in a single page, with additional justification and some detail over the following nine pages. The scope and timeline for the phase-out is summarized below.

Scope of Proposed Phase-Out Policy

With regard to scope of the phase-out policy, the FDA states that although its traditional understanding of LDTs was limited to diagnostics designed, manufactured and used within a single CLIA-certified, high-complexity laboratory, the proposed phase-out policy would be broader, and include IVDs that are manufactured and offered as LDTs by CLIA-certified, high-complexity laboratories. The proposed rule does not clarify what it means to be manufactured and offered as LDTs.

The FDA also proposes that enforcement discretion would continue to apply to certain types of tests, which would not be subject to the phase-out policy. These tests include so-called 1976-type LDTs, tests that use manual techniques without automation; human leukocyte antigen tests; tests for forensic purposes; and tests intended for public health surveillance, each category subject to certain conditions described in the preamble.

Finally, the FDA asserts that certain types of tests were not subject to its enforcement discretion approach for LDTs and accordingly proposes that the phase-out policy would not apply to these tests. Rather, such tests would continue to be subject to FDA regulation as devices. These tests include:

- Direct-to-consumer tests;
- Tests intended for emergency use under Section 564 of the FDCA; and
- Tests intended as blood donor screening or human cells, tissues and cellular- and tissue-based product donor screening tests required for infectious disease testing or for determination of blood group and Rh factors.

Timeline for Phase-Out Policy

The phase-out policy for all in-scope tests would consist of five stages, with each stage marking the end of the FDA's general enforcement discretion policy for different regulatory requirements.

The five stages each begin at a certain time "after FDA publishes a final phaseout policy," which is intended to be published in the preamble to the final rule, as follows:

1. Medical device reporting, and corrections and removal reporting — one year after the final phase-out policy is published.

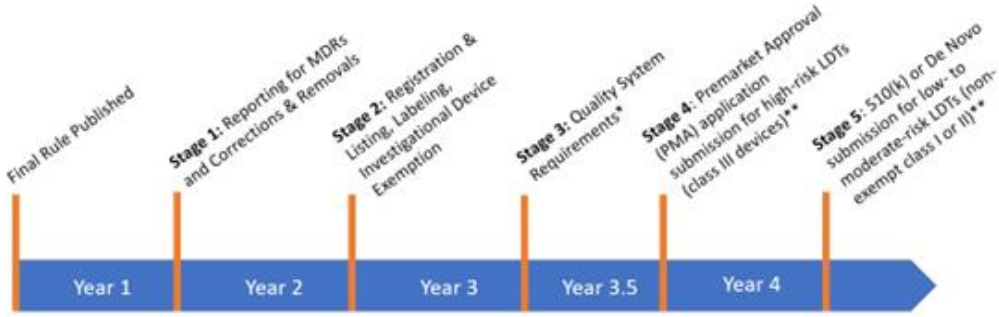
2. Registration and listing, labeling, and investigational use requirements — two years after the final phase-out policy is published.

3. Quality system requirements[1] — three years after the final phase-out policy is published. However, for traditional LDTs, i.e., LDTs that are designed, manufactured and performed within the same CLIA-certified, high-complexity laboratory, only the following quality requirements would apply: design controls, purchasing controls, acceptance activities, corrective and preventative actions, and records.

4. Submission of premarket approval applications for high-risk tests, i.e., Class III devices — three-and-a-half years after the final phase-out policy is published, but no earlier than Oct. 1, 2027. LDTs generally could continue to be offered after this date as long as a premarket approval is under review.

5. Submission of Section 510(k) premarket notifications and de novo requests for moderate- and low-risk tests, i.e., nonexempt Class I and II devices — four years after the final phase-out policy is published, but no earlier than April 1, 2028. LDTs generally could continue to be offered after this date as long as a premarket submission is under review.[2]

A timeline of the phase-out policy is summarized below.



Requests for Comment

While stakeholders may submit comments on any topic associated with the proposed rule, the FDA specifically requested comments on the following topics:

- Whether all or some LDTs should be grandfathered from premarket review or quality system regulation requirements;

- Whether a longer phase-out period should be available for LDTs offered by small laboratories;

- Whether a different policy should apply for LDTs offered by academic medical centers; and

- Whether programs such as New York State's Department of Health Clinical Laboratory Evaluation Program or those within the Veterans Health Administration could be leveraged such that it would be appropriate to continue the FDA's general enforcement discretion for tests in compliance with such programs.

Open Questions

Following publication of the proposed rule, many fundamental questions remain unanswered. These include, but are in no way limited to:

- Are LDTs devices under the FDCA, or does the FDA lack legal authority to regulate LDTs?

- Even if the FDA had authority to regulate LDTs as devices, would such regulation advance the public health as the FDA asserts, or be unduly burdensome without corresponding benefits?

- With regard to scope of the proposed rule, what does it mean to be manufactured and offered as an LDT?

- How would laboratories comply with certain FDA requirements that are inconsistent with the nature of LDTs? As only one example of many, how would a laboratory comply with FDA labeling requirements for a test that is never assembled and distributed?

- Will the FDA publish additional guidance, whether in the preamble to the final rule or elsewhere, with additional detail regarding implementation of the proposed phase-out policy?

- How does this proposed phase-out policy align with other FDA programs? For example, the FDA recently launched a pilot program for companion diagnostic tests used with oncology drug products. Under the pilot program, the FDA would publish recommended minimum performance characteristics for tests intended to be used as companion diagnostics with a particular drug, and the clear implication is that LDTs meeting these performance characteristics would be subject to enforcement discretion even when they make companion diagnostic claims for the drug product. How would LDTs offered under the pilot program be affected by the proposed phase-out policy?

- What would FDA regulation of LDTs mean for manufacturers of instruments, reagents and other tools used by laboratories, including those distributed as research-use-only products?

- How will the proposed rule apply to companies offering bioinformatics or other software utilized by laboratories offering LDTs?

- Will the FDA issue any new or updated policies for in vitro diagnostics in conjunction with the proposed phase-out policy for LDTs?

- Does the FDA have adequate resources to manage implementation of the phase-out policy, if finalized?

Next Steps

The proposed rule was published in the Federal Register on Oct. 3, and comments may be submitted until Dec. 4.

With respect to finalizing the rule, the proposed rule states that the FDA anticipates that Stage 4 of the proposed phase-out policy could begin as early as Oct. 1, 2027, to align with the beginning of the next user fee cycle for devices.

To meet this timeline, the FDA would need to publish the final rule as early as April 1, 2024, a mere five months after the planned close of the comment period. This is a very aggressive timeline for finalizing any rulemaking, and particularly one that would alter the regulatory landscape for an entire field of tests.

Moreover, some stakeholders have already announced that they will request additional time to comment on the proposed rule, which could make the timeline for finalizing the rule even more challenging.

Scott Danzis is a partner and chair of the medical device industry group at Covington & Burling LLP.

Amy Leiser is an associate at the firm.

Wade Ackerman is a partner at the firm.

Covington partner Krista Carver, special counsel Christina Kuhn and partner Gerald Masoudi contributed to this article.

[1] The proposed rule acknowledges that on February 23, 2022, FDA proposed to amend the QSR to align more closely with international consensus standards for devices, currently set forth in ISO 13485:2016, and because FDA intends to finalize these amendments expeditiously, the amended QSR may be in effect before the proposed beginning of stage 3.

[2] The proposed rule anticipates that laboratories may seek to utilize FDA's Third Party review program for these premarket submissions, and suggests that CLIA accreditation organizations potentially could become Third Party reviewers under such program.