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FDA proposes new regulations to increase oversight of Laboratory Developed Tests

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FDA's proposed phased approach to regulating Laboratory Developed Tests (LDTs) presents a seismic shift to the viability of current going-to-market pathways for LDTs.

What's the Impact

- FDA will utilize a more robust regulatory framework that will occur through a "phaseout" period, and will impose additional oversight over LDTs, which may impact how these products are brought to market.
- Although FDA will face obstacles in finalizing the Proposed Rule, the proposal presents a seismic shift to the viability of current going-to-market strategies for LDTs.

On September 29, 2023, the US Food and Drug Administration (FDA) issued its highly anticipated proposed rule that would explicitly regulate laboratory developed tests (LDTs) as medical devices

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(the Proposed Rule). LTDs are in vitro diagnostic products (IVDs) intended for clinical use and designed, manufactured, and used within a single clinical laboratory that meets certain requirements. LTDs have a direct impact on patient care and are used routinely across the healthcare system in a great number of medical decisions. Importantly, most LDTs currently are not reviewed by FDA for clinical validity prior to clinical use. The Proposed Rule intends to clarify that all IVDs—including LDTs—are regulated medical devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act), and reflects FDA's shift in approach to oversight and regulation of laboratories.

FDA's Proposed Rule was promulgated in the backdrop of shifting and confusing FDA guidance documents and policies as well as failed actions by Congress, including the bi-partisan Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2023 (VA23). While the FDA has a long road ahead before it can enforce the changes outlined in the Proposed Rule, the proposal demonstrates the growing consensus among regulators that the existing oversight of LDTs, especially in some settings, may not be sufficient to address the level of risk that these diagnostic products may pose to patient safety.

Current Approach: FDA Enforcement Discretion Policy

The FDA has generally exercised its enforcement discretion over LDTs, meaning that, although the FDA has stated that it has the authority to regulate LDTs, it generally has not enforced any applicable requirements with respect to most LDTs, such as requiring premarket review. Historically, the FDA has deferred oversight of LDTs to the Centers for Medicare and Medicaid Services (CMS), which requires laboratories that manufacture LDTs to comply with the Clinical Laboratory Improvement Amendments of 1988 (CLIA) with testing categories based on the complexity of the method. Laboratories are also subject to state public health licensure laws in many states.

Since the FDA has consistently exercised enforcement discretion and declined to enforce any applicable statutory and regulatory requirements, most LDTs currently on the market have not undergone FDA premarket review. LDTs are typically marketed as being able to diagnose a broad range of diseases, including complex and life-threatening conditions such as cancer, infectious diseases, and genetic disorders. However, studies have shown high variability in LDT performance, leading to potential concerns about LDT validation. The FDA describes that the Proposed Rule is intended to address safety and efficacy concerns of LDTs by requiring them to meet the same standards as other medical devices regulated by the FDA. The FDA's Proposed Rule seeks to accomplish this by (1) amending the IVD definition in the FDA's regulations, and (2) gradually eliminating the FDA's use of its enforcement discretion with respect to LDTs, meaning that LDTs would now have to comply with the FDA's regulatory scheme for medical devices if the Proposed Rule is finalized.

Amendment to the "IVD" Definition

The FDA's Proposed Rule is based on the FDA's view that IVDs—including LDTs—are devices under the FD&C Act, as well as the FDA's view that the FDA has the general rulemaking authority

to regulate LDTs, even if the LDT is "designed, manufactured, and used within a single clinical laboratory."

The FDA is proposing to revise the definition of "in vitro diagnostic products" to make it explicit that IVDs (and thus, LDTs) are devices under the FD&C Act. In other words, IVDs, including LDTs, would fall within the definition of a device in section 201(h)(1) of the FD&C Act, even when they have been manufactured by laboratories. This amendment would reconfirm the FDA's longstanding view that LDTs are devices under the FD&C Act, and, while the FDA has historically exercised enforcement discretion with respect to these devices, the FDA may choose to regulate them, as is now contemplated under the Proposed Rule.

Proposed Phaseout of FDA Enforcement Discretion Policy

This Proposed Rule outlines how the FDA intends to phase out its current enforcement discretion approach so that most LDTs would generally fall under the same enforcement approach as other IVDs, starting from the effective date of the final rule. Under the proposed five-stage phaseout policy, the FDA indicated that it considered certain factors to avoid undue disruption to the testing market, and attempted to create a simple policy that can be easily understood and implemented. Although many questions remain open, we have outlined the proposed phaseout stages below, which the FDA intends to be completed by 2028:

- **Stage 1 (1 Yr. from Final Rule Publication):** The FDA would end its enforcement discretion for the medical device reporting (MDR) requirements under 21 CFR part 803 and the correction and removal reporting requirements under 21 CFR part 806 for all LDTs.
  - The MDR requirements are regulations that require manufacturers of medical devices to report to the FDA any deaths, serious injuries, or certain malfunctions that are caused by or associated with their devices. From the FDA's perspective, these requirements are intended to help the FDA identify and monitor device problems, detect potential device-related public health issues, and facilitate device recalls or other corrective actions. Currently, laboratory services are typically not subject to this level of reporting to the FDA.
- **Stage 2 (2 Yrs. from Final Rule Publication):** The FDA would end its enforcement discretion for the registration and listing requirements under 21 CFR part 807, the labeling requirements under 21 CFR parts 801 and 809, and the investigational use requirements under 21 CFR part 812 for all LDTs.
  - The FDA intends to enforce the applicable regulatory requirements for LDTs, including registration and listing, labeling, and investigational use requirements. Implementation of these requirements would provide the FDA with information on the LDTs offered by laboratories, their intended uses, and their performance characteristics, as well as any adverse events associated with them.
- **Stage 3 (3 Yrs. from Final Rule Publication):** The FDA would end its enforcement discretion for the quality system (QS) requirements under 21 CFR part 820 for all LDTs.
  - Implementation of this stage would ensure that laboratories have a system in place to design, develop, manufacture, and control their LDTs in a manner that ensures their quality and

reliability. In the FDA's view, it would not be in the best interest of the public to phase out the general enforcement discretion approach for QS later than this three-year period, and the Proposed Rule states that compliance with QS requirements is "critical to the quality and validity of LDTs."

- **Stage 4 (3.5 Yrs. from Final Rule Publication):** During this period, but not before October 1, 2027, the FDA would end its enforcement discretion for the premarket review requirements under 21 CFR parts 814 and 860 for LDTs that are classified as "high-risk" devices.
  - Implementation of this stage would require laboratories to submit premarket notifications (510(k)s) or premarket approval applications (PMAs) for their "high-risk" LDTs.
- **Stage 5 (4 Yrs. from Final Rule Publication):** During this period, but not before April 1, 2028, the FDA would end its enforcement discretion for the premarket review requirements under 21 CFR parts 807, 814, and 860 for LDTs that are classified as "moderate-risk" or "low-risk" devices.
  - Implementation of this stage would require laboratories to submit premarket notifications (510(k)s) or de novo requests for their "moderate-risk" or "low-risk" LDTs, and demonstrate that they are substantially equivalent to a legally marketed device.

FDA Retains Existing Approach to Certain Categories of LDTs

Throughout and following the implementation of the proposed phaseout, the Proposed Rule describes how the FDA may continue to use its existing approach to certain LDTs. Specifically, these LDTs include (1) LDTs that the FDA has already excluded from its general enforcement discretion approach, and which continue to require compliance with existing requirements, as reflected by "compliance patterns, multiple public FDA actions and communications, or both;" and (2) LDTs that have been subject to general enforcement discretion because they are otherwise viewed as already subject to sufficient parameters and/or those that may present a lower risk of harm to patient safety. These LDTs include:

- LDTs that are currently regulated by the FDA, for which the FDA does not currently exercise enforcement discretion:
  - **Human cells, tissues, and cellular and tissue-based products (HCT/Ps) LDTs:** LDTS for blood donor screening or HCT/P donor screening required under FDA regulations, such as tests for infectious disease testing of blood donors, tests for determination of blood group and Rh factors, and tests for infectious disease testing of HCT/P donors.
  - **Public Emergency LDTs:** LDTs that are used in potential emergencies, public health emergencies, or for material threats under section 564 of the FD&C Act.
  - **Direct-to-Consumer LDTs:** LDTs that are direct-to-consumer tests, such as tests for genetic risk, wellness, or ancestry where medical professionals, acting as intermediaries, help determine "whether a particular test was appropriate," and assist and help counsel patients on next steps.
- LDT categories for which the FDA proposes to continue general enforcement discretion:
  - **1976-Type LDTs:** LDTs that commonly use manual techniques "performed by laboratory personnel with specialized expertise; use of components legally marketed for clinical use; and

design, manufacture, and use within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing," and for which the FDA has determined that risks have been "sufficiently limited."

- **HLA LDTs:** LDTs that are human leukocyte antigen (HLA) tests that are "designed, manufactured, and used in a single laboratory certified under CLIA that meets the requirements to perform high-complexity histocompatibility testing when used in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing, for HLA antibody screening and monitoring, or for conducting real and 'virtual' HLA crossmatch tests."
- **Forensic Use LDTs:** LDTs intended solely for "forensic (law enforcement) purposes," an approach that the FDA has had in place for 20 years and which the FDA states "applies to such tests regardless of whether they are offered as an LDT."
- **Public Health Surveillance LDTs:** LDTs used exclusively for public health surveillance which are intended solely for use on "systematically collected samples for analysis and interpretation of health data in connection with disease prevention and control" and whose "tests results are not reported to patients or their healthcare providers."

The VALID Act of 2023

On March 29, 2023, Congress proposed VA23, signaling continued public and stakeholder interest in passing legislation aimed at regulating IVDs and LDTs. VA23 and the Proposed Rule have similar goals, and VA23 specifically provides the FDA with the statutory authority to regulate LDTs. VA23, like the Proposed Rule, focuses heavily on concerns related to inaccurate and false results, and seeks to address these issues by implementing a risk-based approach to regulating LDTs. VA23 communicates that the FDA oversight will help ensure the safety and effectiveness of LDTs. Even so, differences exist, including implementation timeline, review pathways, LDTs that are "grandfathered" in, and the law's scope and application. In the Proposed Rule, the FDA acknowledges that the "enactment of such legislation would impact the [Proposed Rule]" and that the FDA will consider the implications of new laws. Should this legislation pass, any differences between VA23 and a final rule from the FDA will require stakeholders to reconcile these requirements.

Conclusion

The Proposed Rule aims to bring LDTs into the same regulatory framework as other diagnostic tools, and phases out the FDA's current enforcement discretion. This will ensure LDTs meet standards of safety and effectiveness.

As the FDA seeks to exercise its rulemaking authority to regulate LDTs in a more expansive way, it seeks comments from laboratories and other stakeholders, which may be submitted here and are due by December 4, 2023. Many questions remain on whether the LDT pathway to market will remain viable, but the devil will be in the details of the final the FDA regulations and any federal legislation.

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