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FDA Final Rule – FDA Takes Action Aimed at Helping to Ensure the Safety and Effectiveness of Laboratory Developed Tests

Fast Facts

- Final Rule Public Notice published April 29, 2024
- This document is unpublished in the Federal Register. It is scheduled to be published on 5/6/2024.
- **Background:** Historically, the FDA has had discretion around enforcement for LDTs. However, most modern LDTs have greater risks associated with them than LDTs used when the FDA's discretion around enforcement was adopted. This updated definition of IVDs also takes into account that there is growing evidence that some IVDs used as LDTs raise public health concerns and have added risks. There are many examples of unsafe, inaccurate, or ineffective IVDs offered as LDTs, which causes obvious concern.
- **Summary**: Due to the changing landscape around LDTs and IVDs used as LDTs, this Final Rule amends the definition of "in vitro diagnostic products" (IVDs) in FDA regulations to state that IVDs are devices under the FD&C Act "**including when the manufacturer of these products is a laboratory**." In addition, the FDA issued a policy today outlining the 4-year phase out of its general discretion approach to LDTs.
- **Effective Date:** 60 days after the date of publication in the Federal Register.
- **Applicability:** This rule will apply to all IVDs, regardless of where they are manufactured. After the four-year phaseout, the FDA will expect all IVDs to meet the same requirements, "though certain IVDs manufactured by laboratories may fall within one of the agency's targeted discretion policy."
- **FDA Guidance:** The FDA also released two draft guidance documents today. 1. An overview of the FDA's thinking about an enforcement discretion policy for "certain unauthorized IVDs for immediate response to an emergent situation, such as an outbreak of an infectious disease, in the absence of a declaration applicable to the IVDs under section 564 of the FD&C Act". 2. The FDA's thinking about considerations "when developing a policy regarding enforcement discretion for certain IVDs during a public health emergency declared under section 564 of the FD&C Act".
- **Related Resources:**
  - Laboratory Developed Tests
  - Laboratory Developed Tests: Frequently Asked Questions
  - FDA LDT Webinars

Concerns over IVDs offered as LDTs

- "Without greater oversight of the safety and effectiveness of LDTs, patients may be more likely to initiate unnecessary treatment, or delay or forego proper treatment based on inaccurate test results or tests promoted with false or misleading claims. This could result in harm, including worsening illness or death, as well as unnecessarily increase health care costs."

Phaseout of the general enforcement discretion

- "Importantly, the FDA considered the large volume of comments received on the notice of proposed rulemaking, and in light of that input, has adjusted the phaseout policy in a manner that better serves the public health."

- "Specifically, the phaseout policy applies 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, and used within such laboratories,20 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."
- The 4-year phaseout approach will be handled in 5 key stages:
    - Stage 1: "beginning 1 year after the publication date of this final rule, FDA will expect compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198."
    - Stage 2: "beginning 2 years after the publication date of this final rule, FDA will expect compliance with requirements not covered during other stages of the phaseout policy, including registration and listing requirements, labeling requirements, and investigational use requirements."
    - Stage 3: "beginning 3 years after the publication date of this final rule, FDA will expect compliance with QS requirements under part 820 (other than requirements already addressed in stage 1)."
    - Stage 4: "beginning 3½ years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for high-risk IVDs offered as LDTs, unless a premarket submission has been received by the beginning of this stage in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review."
    - Stage 5: "beginning 4 years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for moderate-risk and low-risk IVDs offered as LDTs (that require premarket submissions), unless a premarket submission has been received by the beginning of this stage in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review."
- This four-year phaseout approach is meant to protect the public health by assuring safe and effective uses of these tests without disrupting patient care.

Enforcement Discretion

Please note that there are important caveats associated with the categories of enforcement discretion. Laboratories who believe that a LDT may fall within an area of enforcement discretion are encouraged to carefully review the rule and any related guidance documents and to consider consultation with the FDA.

- **Enforcement Discretion Policies with Respect to All FDA Requirements:** "For several categories of tests, FDA intends to continue the general enforcement discretion approach and generally not enforce any applicable requirement because tests in these categories are, in our experience, unlikely to pose significant risks or are conducted in circumstances that themselves will mitigate the risks.":
    - **1976-Type LDTs** – LDTs with characteristics common to LDTs offered in 1976, including:
        - "Use of manual techniques (without automation) performed by laboratory personnel with specialized expertise"
        - "Use of components legally marketed for clinical use"
        - "design, manufacture, and use within a single CLIA-certified laboratory that meets the requirements under CLIA for high-complexity testing"

- **Human Leukocyte Antigen (HLA) tests** that "are designed, manufactured, and used within 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 typing, for HLA antibody screening or monitoring, or for conducting real and "virtual" HLA crossmatch tests…"
- **Forensic Tests for Law Enforcement Purposes** – "Tests used in the law enforcement setting are subject to Protections and requirements associated with the judicial process that mitigate risk related to test accuracy and sample collection and that generally are not available in the home, workplace, insurance, and sports settings."
- **Department of Defense (DoD) or Veterans Health Administration (VHA) LDTs** – "LDTs manufactured and performed within DoD or VHA. This policy applies only to LDTs used for patients that are being tested and treated within DoD or VHA."

- **New York State Clinical Laboratory Evaluation Program (NYS CLEP)**
  "FDA also generally intends to exercise enforcement discretion with respect to premarket approval requirement for LDTs that are approved by NYS CLEP…FDA intends to phase out the general enforcement discretion approach with respect to other applicable requirements for these tests…"

- **Enforcement Discretion Policies with Respect to Premarket Review and Certain Quality System (QS) Requirements:** "FDA also intends to exercise enforcement discretion and generally not enforce premarket review and most QS requirements for three categories of IVDs."
  - **Unmet Needs**: "…LDTs manufactured and performed by a laboratory integrated within a health care system to meet an unmet need of patients receiving care within the same health care system…FDA intends to phase out the general enforcement discretion approach for these LDT with respect to all other applicable requirements…FDA considers an LDT to be for an unmet need where there is no available FDA-authorized IVD that meets the patient's needs."
  - **Currently marketed IVDs** offered as LDTs that were first marketed prior to the date of issuance of the final rule. This enforcement discretion policy is intended to address the risk that the perceived costs of compliance with such requirements could lead to the widespread loss of access to beneficial IVDs on which patients currently rely.
  - **Non-molecular Antisera LDTs for rare RBC Antigens:** "when such tests are manufactured and performed by blood establishments, including transfusion services and immunohematology laboratories and when that is no alternative IVD available to meet the patient's need for a compatible blood transfusion. This policy does not apply to molecular tests used for genotyping RBS antigens."

Increased Compliance

- With this new rule, IVDs will be held to the same device requirements, including premarket review, adverse event reporting and quality system requirements. This will improve the confidence in IVDs with patients and health care providers.
- In addition, this means the FDA will also now be able to oversee adequate representation in validation studies and increased transparency around the performance of the IVD, which may improve health equity.

Potential Impacts

- This final rule will impact manufacturers of IVDs, including labs, and those who perform research with IVDs used as LDTs. Within the phaseout policy framework, researchers using IVDs will now need to consider the FDA requirements around utilizing a device in their studies, including IDE requirements and the requirements of 21 CFR 50 and 56, when applicable. See Section 10 in the Other Legal Comments section within the FDA Responses to Comments section of the preamble for discussion about clinical investigations and about Research Use Only (RUO) tests.
- HRPPs and IRBs may need to update their policies and procedures and provide training and resources for researchers, staff, and IRB members.
- As there are caveats and exceptions to this new rule, it will be important to familiarize yourself with the preamble to the Rule, and the resources and draft guidance documents from the FDA.