Inside FDA's Proposed Rule to Regulate LDTs

Key questions labs should consider now

THE FDA GROUP LLC

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Introduction

In Fall of 2023, the FDA *proposed a rule* to end its enforcement discretion policy for laboratory-developed tests (LDTs) by treating them as In Vitro Diagnostics (IVDs) subject to regulatory requirements as medical devices.

The rule would add ten words to the definition of "in vitro diagnostic products" in 21 CFR Part 809.3(a), stating that IVDs are considered devices under the FDCA, even if a laboratory is a manufacturer (revisions underlined):

> ***"In vitro diagnostic products are those 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. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act, including when the manufacturer of these products is a laboratory."***

The rule proposes a phased approach, with LDT manufacturers required to comply with regulatory requirements in stages. Compliance will begin one to four years after the final LDT rule is published. The final policy will be included in the rule's preamble, and the proposed rule, as it stands as of the publishing of this paper in December 2023, does not intend to "grandfather" any LDTs that are currently available in the market. It's also currently unclear when the regulatory requirements will become effective.

Opponents of the proposed rule are likely to ramp up their lobbying of Congress to prevent the rule from being finalized. If the rule is finalized, they will likely try to stop or stall the rule through litigation.

The comment period for the FDA's proposed rule closed on 4 December. To date, the agency says it has received more than 6,700 comments, though it has only posted fewer than 4,000 of those comments to the public docket, and only 500 of those comments are viewable at the time of this publication.

Advocates for the proposed rule argue that the FDA should oversee these tests, particularly in cases where test results impact life or death situations. They also assert that regulating LDTs would ensure a level playing field between labs that develop such tests and traditional IVD manufacturers.

However, labs and their supporters argue that the FDA lacks the legal authority to regulate such tests. They also believe that regulating LDTs would impede patient access to them.

While it remains to be seen if and to what degree more LDT oversight is coming, the FDA wasted no time *updating its Unified Agenda* to indicate that a final rule may be published as soon as April 2024. Given the volume of comments filed and the agency's tendency to miss its own stated dates, it's important to take this ambitious timeline with a grain of salt.

Many of the comments were comprehensive, detailed critiques of the proposed rule—and under the Administrative Procedure Act, the FDA is obligated to address major substantive issues when it publishes a final rule. Complying with that requirement between now and April will be a daunting task. But, FDA has expressed urgency in moving forward with this rule so it is not out of the question that it could happen.

The end of enforcement discretion

The proposed rule would phase out LDT enforcement discretion over a period of four years, after which most LDTs will be subject to all applicable medical device regulatory requirements.

The phase-out period would apply to LDTs currently on the market in reliance on the FDA's enforcement discretion policy ("affected laboratories"). It would not extend to tests for which the FDA has historically not exercised enforcement discretion (e.g., direct-to-consumer tests, tests for use in a public health emergency).

The FDA proposes a five-stage transition period for all affected laboratories currently who are not subject to one of the areas of continued enforcement discretion:

STAGE 1 One year after the final rule is issued	Labs must begin filing medical device reports (MDR) under 21 C.F.R. Part 803 and notices of correction and removal under 21 C.F.R. Part 806.
STAGE 2 Two years after the final rule is issued	Labs must register with FDA as a device establishment and list LDTs performed, pursuant to 21 C.F.R. Part 807. Labs must also begin complying with device labeling requirements (21 C.F.R. Part 801) and investigational device exemption requirements (21 C.F.R. Part 812).
STAGE 3 Three years after the final rule is issued	Labs must comply with the Quality System Regulation (QSR) (21 C.F.R. Part 820).
STAGE 4 Three and a half years after the final rule is issued	Labs offering high-risk LDTs (i.e., Class III) would be required to submit an application for premarket approval (PMA) to FDA.
STAGE 5 Four years after the final rule is issued	Labs offering low and moderate-risk LDTs (i.e., Class I or II) would be required to submit a 510(k) premarket notification, unless eligible for exemption.

Can the FDA actually pull this off?

One of the initial questions is whether or not the FDA will be able to implement this rule.

One of the central challenges presented is whether or not the FDA has the statutory authority to regulate LDTs in the first place. Some argue that the Federal Food, Drug, and Cosmetic Act simply did not confer that power upon FDA. While Congress has considered legislation that would have given the FDA that authority, it never did so. Some opponents argue that the FDA cannot now unilaterally assume power that Congress chose not to confer. *This 60-page comment* made on behalf of the Coalition to Preserve LDT Access and Innovation offers an in-depth legal argument for a lack of statutory authority.

The FDA faces several other challenges, too:

- **An overly ambitious timeline:** The FDA's proposed rule aims for a quick finalization, but considering the volume and complexity of comments, this is seen as overly optimistic. Complying with the Administrative Procedure Act's requirement to address all major substantive issues adds to this complexity. Requiring labs to adapt to new Quality System Regulations (QSR) within a three-year timeframe is another challenging prospect, especially without a final rule in place.
- **Inaccurate laboratory estimates:** The FDA's estimate of 12,000 CLIA-certified high-complexity labs, based on a 2018 review, is outdated. Current numbers from the CLIA database show 17,206 labs, indicating a significant underestimation.
- **Underestimation of LDT volume:** The FDA's projection of 80,000 LDTs is likely lower than the actual figure. With an understated number of labs and a per-lab test count, the true number of LDTs could exceed 100,000.
- **Unprecedented premarket submission volumes:** The FDA anticipates a vast number of submissions, including 32,160 510(k) notifications and over 4,000 each of PMAs, PDPs, and de novo submissions. This volume far exceeds the agency's historical averages and will require a massive increase in staffing and training.

- **Challenges in LDT classification and exemption assumptions:** The FDA's assumptions about LDT classifications and exemptions may not align with the novel and complex nature of these tests, potentially leading to an overestimation of exempt LDTs.
- **Third-party review program limitations:** Reliance on the Third-Party Review Program, which is underutilized and not commonly used by the IVD industry, is unlikely to significantly reduce the FDA's workload.
- **Staffing and recruitment issues:** The anticipated high volume of submissions will necessitate a considerable expansion of FDA staff, creating competition for qualified regulatory affairs professionals. This competition could exacerbate hiring challenges and increase costs.

If the FDA doesn't adequately prepare for implementing its LDT regulation, it may either have to stop reviewing non-LDT premarket submissions or face significant delays in implementing the final rule. Given the ongoing MDUFA VI negotiations and the industry's likely intolerance for halted reviews, it's probable that the FDA will need to extend the timelines for LDT premarket submission reviews to match their resources. Acknowledging this situation and extending implementation timelines would be more practical for all parties involved.

Preliminary questions for Stage 1

While it remains to be seen if the FDA can hit this date, we thought it's worth presenting the preliminary questions impacted labs will need to consider if they have only a year to hit the Stage 1 requirements once that final rule is issued: Begin filing medical device reports (MDR) under 21 C.F.R. Part 803 and notices of correction and removal under 21 C.F.R. Part 806.

To conduct a high-level gap analysis and understand the work projects involved in hitting this milestone, we've identified a number of questions labs will need to consider.

21 C.F.R. Part 803 (Medical Device Reporting)

Reporting Mechanisms (Medical Device Reporting)

- **Do we have a system in place for identifying and reporting adverse events and product problems?** Per 21 C.F.R. 803.17, labs must develop, maintain, and implement written MDR procedures for the timely and effective identification, communication, and evaluation of events that may be subject to medical device reporting requirements. Labs will need a structured process or system, ideally integrated with the QMS, that flags potential adverse events and product problems.
- **How effective is our current method of capturing data that could indicate a reportable event?** The requirement for effective event capture is implicit in the need to comply with the reporting obligations laid out in 21 C.F.R. 803.50, which stipulates the criteria for reportable events. Evaluate whether current data-capturing methods are consistently identifying potential reportable events. We suggest reviewing historical data to see if any reportable incidents were missed and analyzing the sensitivity and specificity of those detection methods.

THE FDA GROUP RECOMMENDS

- ☐ Implement a digital reporting system, ensuring it's integrated with your existing QMS for seamless data flow.
- ☐ Conduct interactive workshops for staff, emphasizing the importance of prompt and accurate identification of adverse events and product issues.
- ☐ Regularly review and update the system in line with any changes in 21 C.F.R. 803.17, incorporating new types of events or reporting criteria as necessary.
- ☐ Perform a detailed audit of your current data capturing methods, focusing on how well they align with 21 C.F.R. 803.50 criteria.
- ☐ Use historical data to test the effectiveness of your current system – analyze missed incidents and adjust detection methods accordingly.
- ☐ Implement technology solutions like automated flagging or alert systems to enhance the sensitivity of data capture.

Event Categorization

- **Are we correctly identifying what constitutes a reportable event under FDA guidelines?** 21 C.F.R. 803.50 outlines what constitutes a reportable event, detailing the criteria for reporting deaths, serious injuries, and malfunctions. Create and keep updated a reference guide or decision tree that outlines what constitutes a reportable event based on these guidelines.
- **Do we have clear criteria to distinguish reportable from non-reportable events?** This is based on the definitions and criteria provided in 21 C.F.R. 803.50. Develop clear, written criteria and examples to help staff differentiate between reportable and non-reportable events. Implement a review process for borderline cases, potentially involving a compliance officer or regulatory expert.

THE FDA GROUP RECOMMENDS

- ☐ Develop a comprehensive decision tree or reference guide that clearly outlines FDA criteria for reportable events. Ensure this is easily accessible to all staff.
- ☐ Conduct regular training sessions, using real-life scenarios to help staff understand and apply these guidelines in their daily operations.
- ☐ Create detailed written criteria with illustrative examples to guide staff. This should be a part of your SOPs.
- ☐ Establish a committee or a panel for reviewing ambiguous cases.

Staff Awareness and Training

- **How will we ensure relevant staff members are aware of the FDA's requirements for medical device reporting?** While specific training requirements are not detailed in 21 C.F.R. Part 803, the effective implementation of these regulations implicitly requires staff awareness and understanding. Regulators will be looking for a training program.
- **How will we ensure staff members have been adequately trained on how to identify and report adverse events?** This is an extension of the procedural requirements in 21 C.F.R. 803.17. Make sure your training programs include real-world examples and simulations.

THE FDA GROUP RECOMMENDS

- ☐ Develop an in-depth training program focused on the FDA's medical device reporting requirements, using a mix of online courses, in-person sessions, and printed materials.
- ☐ Incorporate interactive training modules, including scenario-based exercises and role-playing, to simulate real-world situations.
- ☐ Provide access to a repository of case studies and past incidents to help staff understand the nuances of identifying and reporting adverse events.

Documentation and Record-Keeping

- **Do we have a robust system for documenting adverse events and the decisions made about reporting them?** Per 21 C.F.R. 803.18, facilities are required to maintain records of all information relating to adverse event reporting. Labs should implement a centralized documentation platform that logs all adverse events, the investigation process, and decisions regarding reporting. Make sure the system allows for detailed entries, including timelines, event descriptions, impact assessments, and follow-up actions.
- **Are these records easily accessible and organized for potential FDA inspection?** 21 C.F.R. 803.18 also requires that these records be accessible for inspection and copying by the FDA. Labs will need to maintain an organized and up-to-date record-keeping system, preferably digital, for easy retrieval during inspections. We always suggest using a filing system that categorizes records logically, such as by date, product, or type of event.

THE FDA GROUP RECOMMENDS

- ☐ Implement a centralized, electronic documentation system that is user-friendly and allows for comprehensive entries, including event descriptions, investigation processes, and decision rationales.
- ☐ Train staff on thorough documentation practices, emphasizing the importance of detail and accuracy for regulatory compliance and internal audits.
- ☐ Utilize a digital record-keeping system with robust search and categorization capabilities.
- ☐ Regularly update and back up the system.

Quality and Timeliness of Reports (Medical Device Reporting)

- **How will we ensure the reports we generate are comprehensive and meet all the FDA's requirements for content and detail?** 21 C.F.R. 803.52 lists the specific information that must be included in medical device reports, including:
    - Patient information
    - Adverse event or product problem
    - Device information
    - Initial reporter information
    - Reporting information for all manufacturers
    - Device manufacturer information

  Make sure reports include all necessary information as dictated by the FDA, such as specific details of the event, affected product, patient outcome, and corrective actions taken. Implement a quality check process where reports are reviewed by a compliance officer or team before submission to the FDA.
- **How will we ensure we meet the FDA's timelines for reporting adverse events?** 21 C.F.R. 803.50 and 803.53 outline the time frames within which reports must be submitted to the FDA. Establish internal deadlines that are tighter than the FDA's to create a buffer for unforeseen delays.

803.50:

If you are a manufacturer, you must report to us the information required by § 803.52 in accordance with the requirements of § 803.12(a), no later than 30 calendar days after the day that you receive or otherwise become aware of information, from any source, that reasonably suggests that a device that you market…

803.53:

You must submit a 5-day report to us with the information required by § 803.52 in accordance with the requirements of § 803.12(a) no later than 5 work days after the day that you become aware that:

(a) An MDR reportable event necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. You may become aware of the need for remedial action from any information, including any trend analysis or

(b) We have made a written request for the submission of a 5-day report. If you receive such a written request from us, you must submit, without further requests, a 5-day report for all subsequent events of the same nature that involve substantially similar devices for the time period specified in the written request. We may extend the time period stated in the original written request if we determine it is in the interest of the public health.

- **Do we have procedures for follow-up actions after an adverse event report or a correction/removal notice has been filed?** This should include monitoring the effectiveness of corrective actions and maintaining communication with the FDA if necessary.

THE FDA GROUP RECOMMENDS

- ☐ Create a checklist of required information per 21 C.F.R. 803.52. Ensure the checklist covers all aspects, including patient, event, device, and manufacturer information.
- ☐ Establish a quality review team to check reports before submission.
- ☐ Set internal deadlines stricter than FDA requirements.
- ☐ Monitor adherence to these deadlines.
- ☐ Develop a process for post-reporting follow-ups and effectiveness monitoring of corrective actions. This process should include periodic reviews and updates based on the outcomes and feedback.
- ☐ Maintain communication with the FDA as required. Assign a dedicated point of contact for FDA communications.

21 C.F.R. Part 806

Identification of Corrections and Removals

- **Do we have a clear understanding of what constitutes a correction or removal that must be reported to the FDA?** 21 C.F.R. 806.10(a) details the circumstances under which corrections and removals must be reported to the FDA. Define clearly in internal policies what constitutes a correction or removal that must be reported, aligning with FDA definitions.
- **Are there procedures in place to identify and document such actions?** Establish an SOP for identifying, assessing, and documenting corrections and removals. Include a checklist or form that captures all necessary information about the event to be completed for each incident.

THE FDA GROUP RECOMMENDS

- ☐ Develop clear internal policies aligned with FDA definitions. Involve legal and compliance teams in policy development to ensure accuracy and completeness.
- ☐ Regularly review and update these policies. Setting a fixed schedule for policy review ensures consistency and compliance.
- ☐ Establish an SOP for documenting corrections and removals. Include a detailed form or checklist to capture all relevant information.
- ☐ Implement a checklist or form for each incident.

Decision-Making Process

- **Is there a clear decision-making process for determining when a correction or removal needs to be reported to the FDA?** This is an interpretation of the requirements in 21 C.F.R. 806, which implies a process to evaluate and report corrections and removals. Create a flowchart or decision tree that guides the decision-making process, outlining criteria for when a correction or removal needs to be reported to the FDA. Make sure the process includes steps for escalation and review by higher authorities when needed.

- **Who will be responsible for making these decisions, and do they have the necessary information and authority?** Assign specific roles and responsibilities for decision-making regarding corrections and removals (typically to a regulatory affairs or quality assurance team).

THE FDA GROUP RECOMMENDS

- ☐ Design a flowchart that outlines the decision-making process for reporting corrections and removals.
- ☐ Include escalation and review procedures.
- ☐ Assign roles for decision-making to specific teams like regulatory affairs. Provide training to these teams to ensure they understand the criteria and process.
- ☐ Ensure they have access to necessary information.

Communication Protocols

- **Do we have a protocol for communicating corrections or removals internally and, if necessary, to the FDA?** While not explicitly stated in 21 C.F.R. 806, effective communication is essential to ensure compliance with these regulations. Develop a communication plan for how and when to notify internal stakeholders and the FDA about a correction or removal.
- **How do we ensure that all relevant parties are informed of a correction or removal?** Set up a notification system to inform all relevant parties, including departments like manufacturing, quality control, and distribution, about a correction or removal. Include a process for updating external stakeholders, such as suppliers or customers, if necessary.

THE FDA GROUP RECOMMENDS

- ☐ Develop a plan detailing how and when to communicate internally and with the FDA. Include scenarios and templates for communications to ensure consistency.
- ☐ Train staff on these communication protocols.
- ☐ Set up a notification system for internal and external stakeholders.

Documentation Standards

- **Are we maintaining proper documentation for each correction or removal, including the rationale for the action and whether it was reported to the FDA?** 21 C.F.R. 806.20 requires firms to keep records of corrections and removals, including a record of the reason for the correction or removal and the quantity of devices corrected or removed. Use a standardized form or template to ensure consistency in documentation.
- **Are these records organized and readily accessible for review?** Implement a filing system, preferably digital, that categorizes records for easy retrieval during internal reviews or FDA inspections. Regularly update and backup records to ensure their integrity and availability.

THE FDA GROUP RECOMMENDS

- ☐ Use standardized forms or templates for consistency.
- ☐ Regularly review and update these templates to ensure they remain relevant and comprehensive.
- ☐ Implement a digital, categorized filing system.
- ☐ Conduct regular checks to ensure accessibility and organization. Use a checklist to ensure all key aspects of record-keeping are reviewed.

A few general questions

- **How are adverse event reporting and correction/removal processes integrated with your broader risk management strategy?** Ensuring that these processes are part of an overall risk management framework can help in early detection and more effective handling of potential issues. Develop a risk management framework that includes adverse event reporting and correction/removal processes. Conduct regular risk assessments to identify potential areas of risk related to medical devices and integrate findings into the adverse event reporting system.
- **How do we ensure that our vendors and suppliers are compliant with these FDA requirements, and how does this impact our reporting and correction/removal processes?** Since many labs work with external vendors and suppliers, their compliance is also critical—and ultimately the lab's responsibility. Implement a vendor management program that includes evaluating and monitoring the compliance of vendors and suppliers with FDA requirements. Make sure to include compliance clauses in contracts with vendors and suppliers, and conduct regular audits of vendors and suppliers to ensure ongoing compliance.
- **How is feedback from staff, audits, and regulatory inspections used to improve the adverse event reporting and correction/removal processes?** Continuous improvement is key to maintaining compliance and enhancing the effectiveness of these processes. Establish a feedback mechanism where staff can report observations or concerns related to adverse event reporting and correction/removal processes.

A high-level implementation strategy

Here's a high-level plan for ensuring compliance with medical device reporting under 21 C.F.R. Part 803 and notices of correction and removal under 21 C.F.R. Part 806 (Stage 1 Requirements):

1. Review current incident and adverse event reporting mechanisms.
2. Identify gaps in capturing data required for FDA medical device reporting.
3. Create or refine procedures for reporting adverse events and corrections or removals in compliance with FDA requirements. Train on those procedures.
4. Set up systems for capturing, documenting, and reporting relevant information to the FDA.
5. Establish a timeline for regular review and updates.
6. Ensure proper documentation of all reports and actions taken for compliance and future audits.

Given the ambitious timeline proposed by the FDA, are you prepared to efficiently align your operations to meet each stage of the phase-out period if the rulemaking goes forward? Have you identified a consulting firm that can help you move quickly and access the experts we need to meet these deadlines?

How The FDA Group can help

We're here to turn uncertainty into a pathway for growth and compliance in what will most likely be a more highly regulated future. Our tailored services are designed to navigate the complexities of the proposed rule, ensuring your LDTs meet regulatory expectations without losing the innovative edge that sets you apart.

Here's how we can help impacted firms take action now:

1. Regulatory gap assessment and strategic planning

We begin with a thorough gap analysis to pinpoint your current position against the looming FDA rulemaking. This process is not just about identifying shortcomings; it's about uncovering opportunities for regulatory excellence and market leadership.

2. Compliance framework development

Transitioning your LDTs to comply with FDA, IVDR, ISO 13845, and CE standards can be daunting. Our team crafts a bespoke regulatory framework for your tests, ensuring you're not just ready for today's standards but also poised for tomorrow's challenges.

3. Submission and registration guidance/support

Navigating the FDA's submission process requires expertise and precision. We guide you through every step, preparing submission packages and offering hands-on support during the process to ensure your LDTs achieve regulatory acceptance.

4. Continuous regulatory vigilance

Regulatory landscapes are never static, and FDA's LDT rulemaking is actively in progress. Our continuous improvement protocols keep you ahead of the curve, ensuring that your compliance is not just a one-time achievement but a sustained competitive advantage.

Learn more and connect with us.

Learn more about our services and contact us today to take the first step toward ensuring your next project is completed successfully—on time and on budget.

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Who is The FDA Group?

The FDA Group helps life science organizations rapidly access the industry's best consultants, contractors, and candidates. Our resources assist in every stage of the product lifecycle, from clinical development to commercialization, with a focus in Quality Assurance, Regulatory Affairs, and Clinical Operations.

Whether you need project support or need to fill a single role or multiple roles on your team, we connect you to life science professionals with experience and expertise across functions, product lifecycle phases, and locations to augment and scale your team through consulting projects, staff augmentation, and FTE recruitment.

We help thousands of firms, including 17 of the top 25 global pharmaceutical, biotech, and medical device companies, find the resources they need, when and where they need them, through the optimal workforce model. Our resources are located in several dozen countries and have expertise throughout the life sciences. All of our services are backed by a Total Quality Guarantee.