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FDA's Lab-Developed Test Rule May Bring Historic Challenges

By **Stacy Amin** (November 8, 2023, 6:06 PM EST)


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At the end of September, the U.S. Food and Drug Administration released a proposed rule that sounds mundane — its plan to regulate laboratory-developed tests — but was the administrative law equivalent of Taylor Swift announcing her Eras tour.

The proposed rule[1] would finally clarify that the FDA can and will regulate laboratory-developed tests, or LDTs, as any other medical device. When finalized, the rule could spark the most significant litigation the agency has faced in over 20 years, with ramifications far beyond laboratories.

For decades, the FDA has exercised what it calls enforcement discretion with respect to most LDTs, i.e., it generally has not enforced regulatory requirements with respect to most in vitro diagnostic products designed, manufactured and used within a single laboratory.

At the time that the FDA adopted this approach many decades ago, LDTs were generally made in small volumes by laboratories that served their local communities, employed manual techniques and were performed by laboratory personnel with specialized expertise.

In the proposed rule, the FDA says that it has witnessed an explosion in the volume, complexity and scope of tests offered as LDTs. Today's LDTs are often manufactured by corporations that run large volumes of tests available nationwide, rely on high-tech instrumentation and software, and are used to diagnose or screen for serious diseases.

As justification for the proposed rule, the FDA has raised numerous significant concerns about these practices, including high rates of false positives and false negative results, laboratories failing to perform adequate validation studies, and reports of adverse events leading to tragic unnecessary interventions and missed treatment opportunities.

The accuracy of testing is particularly important as more and more novel treatments rely on testing as the primary driver of therapeutic decisions. Moreover, the FDA says that LDTs are often indistinguishable from the in vitro diagnostic developed by commercial laboratories that are subject to the FDA's regulatory requirements, creating an arbitrary regulatory bifurcation and a disincentive to develop tests that undergo regulatory review.

The FDA proposes to amend its regulations to clarify that in vitro diagnostics are devices under the Federal Food, Drug and Cosmetic Act when the manufacturer of those products is a laboratory.

The definition of "in vitro diagnostic products for human use" currently says, "These products are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetics Act."

The proposed rule would add to the end of that definition, "including when the manufacturer of these products is a laboratory." This simple change in the regulatory definition would clarify that laboratories are subject to the full panoply of medical device requirements, including registration and listing, adverse event reporting, quality systems requirements and premarket review.

The FDA proposes to phase out its general enforcement discretion policy in five stages:

- Phase 1: Beginning one year after a final rule is issued, LDT manufacturers would have to comply with adverse event reporting requirements and correction and removal reporting requirements.

- Phase 2: Beginning two years after a final rule, FDA will enforce registration and listing, labeling and investigational use requirements.

- Phase 3: Beginning three years after a final rule, FDA will enforce Quality System requirements. For labs certified by the Clinical Laboratory Improvement Amendments, if their LDTs are not distributed outside the lab in which all manufacturing activities occur, a more limited number of Quality System requirements will be enforced. The FDA also noted that it intends to finalize its proposed amended QS requirements before the beginning of Stage 3.

- Phase 4: Beginning three-and-a-half years after a final rule, but not before Oct. 1, 2027, the FDA would enforce premarket review requirements for high-risk in vitro diagnostics, i.e., those requiring a premarket approval. This would align the beginning of premarket review with the beginning of the next user fee cycle. The FDA proposes not to enforce against tests offered as LDTs while a premarket approval is pending review.

- Phase 5: The general enforcement discretion approach for remaining IVDs, including moderate-risk and low-risk LDTs, would end four years after publication of a final rule, but not before April 1, 2028.

The proposed rule, if finalized, is certain to provoke some of the most interesting, and precedent-setting, legal challenges the FDA has seen in decades, and the outcome will likely reverberate across the agency's product centers.

For starters, this rulemaking comes at a time when skepticism of government regulation is at perhaps an all-time high. The U.S. Supreme Court is hearing at least one case this term, Loper Bright Enterprises v. Raimondo,[2] in which it is reviewing whether to continue giving agencies Chevron[3] deference for their interpretations of ambiguous terms in statutes.

Certainly the FDCA definition of medical device is ambiguous, and traditionally Chevron deference for the FDA's interpretation in rulemaking would mean the FDA's interpretation wins the day. That is far from certain with Loper on the horizon, and a lawsuit against a final rule on LDTs may be the first significant challenge to the FDA's regulatory authority in the wake of whatever regime is in place after Loper is decided.

Anyone with an interest in the FDA's ability to regulate new scientific and technological developments,

or ability to take action against rogue and illicit markets, should be concerned about how precedent gets set in any future LDTs litigation.

The FDA also likely must combat arguments that laboratories have a substantive reliance interest in enforcement discretion. Since the Supreme Court's 2009 decision in FCC v. Fox Television,[4] agencies have been required to weigh the reliance interests of regulated parties when changing policy in a rulemaking.

However, that case did not directly address reliance on enforcement discretion policies. With the Supreme Court's 2020 decision in U.S. Department of Homeland Security v. Regents of the University of California,[5] in which the court held it was arbitrary and capricious for the Trump administration to revoke the Deferred Action Childhood Arrival enforcement discretion program, the FDA has had to grapple with the extent to which regulated parties may have a reliance interest in its enforcement discretion policies.

To what extent courts might recognize a reliance interest of the lab industry in an informal agency practice, and to what extent that interest can supersede the agency's broad statutory authority, is a developing area of law and of great uncertainty to the FDA and other agencies.

The proposed rule delves into one of the most detailed and fascinating history lessons in any FDA rulemaking. The history of the FDA's regulation of LDTs is not just important to put the rulemaking in context, but more likely, is provided in detail to support the legal basis for the rule.

Establishing that throughout the FDA's history, the FDA has always asserted its jurisdiction over LDTs and has always regulated LDTs to some extent, is important to counter any reliance arguments the industry may raise in litigation.

The history lesson is important to counter another argument that may be raised against the rule — that the rulemaking may present a major-questions problem. The major-questions doctrine has been popular to raise at the Supreme Court in recent years, and there are many debates[6] as to whether it is a canon or an interpretive tool and whether it requires Congress to delegate in highly specific terms.

In the context of the regulation of LDTs, the issue can be simplified as whether the statute needs to speak specifically and clearly to the agency's authority to regulate LDTs. This argument is especially likely to be raised in the context of Congress' failure to pass the VALID Act into law, which would have provided clarity and a new regulatory construct for the FDA's oversight of LDTs.

How the resurgence of the major-questions doctrine may affect the FDA was widely discussed after Supreme Court cases West Virginia v. EPA[7] last year and Biden v. Nebraska[8] this year raised questions about whether the FDA's broad delegation of authority in the 1930s to regulate new product areas could be curtailed.

The impending litigation over this rule may pose the first major-questions doctrine case for the FDA since the original Supreme Court case that articulated the doctrine, FDA v. Brown & Williamson Tobacco Corp. in 2000.[9]

The FDA's intricate breakdown of every footnote, statement, letter, etc., over 30 years asserting its authority, and Congress' acknowledgment of that authority, is important to counter a major-questions argument.

However, if the doctrine requires a clear statement of authority, as articulated by Justice Neil Gorsuch in West Virginia v. EPA, then arguably vast swaths of FDA's current and future regulatory jurisdiction are at risk.

Regardless of whether constitutional arguments are invoked, challengers are certain to argue that the FDA exceeded its statutory authority in adopting the rulemaking.

The clinical laboratory industry and research institutions have long argued that the Centers for Medicare and Medicaid Services regulates laboratory developed tests through CLIA and that LDTs are not a product and are instead a service that constitutes the practice of medicine, outside the FDA's purview.

These arguments are sure to get extra support by the September decision from the U.S. Court of Appeals for the Fifth Circuit in Apter v. Department of Health & Human Services,[10] in which the court of appeals allowed a case against the FDA to go forward, alleging that the FDA acted outside its authority by interfering with the practice of medicine.

The FDA has preemptively addressed those arguments in the proposed rulemaking. The FDA argues that while CMS establishes requirements for laboratories and laboratory personnel, it does not regulate critical aspects of tests' development, such as performance of the test, clinical validity, manufacturing quality, design controls, human subject protection for those involved in trials or adverse event reporting.

The FDA argues that it has the jurisdiction and the expertise to regulate this industry. It also argues that the practice-of-medicine exemption in the FDCA only applies to the use of legally approved devices, not devices that have foregone review altogether.

The proposed rulemaking goes to great effort to address potential Administrative Procedure Act arguments that the rule is arbitrary and capricious. Those opposed to the rule will contend that the FDA underestimated the costs of the rulemaking, overestimated the benefits and overestimated its ability to manage an influx of marketing applications.

During the comment period, opposed stakeholders will likely generate reams of evidence in support of those arguments, saying the rulemaking will decimate the industry. They will argue that CMS and other state regulators adequately regulate the tests now, so the additional costs are unjustified. They will combat the evidence of public health harms in the rulemaking by claiming them to be anecdotal, and provide their own evidence of the benefits of consumer and doctor choice.

The FDA has likely already provided the best evidence it has to support the rule. Whether the ultimate rulemaking will survive an arbitrary and capricious challenge may depend on the strength of the evidence submitted by its opponents, and the strength of the evidence its supporters submit.

It has been demonstrated time and again that those who are opposed to FDA regulation of LDTs will marshal substantial resources to kill any efforts to impose greater oversight of the industry.

It is unclear whether those who support the rulemaking are up to the task of defending it. Many stakeholders who supported previous legislative efforts did so behind the scenes, and ultimately those efforts were not enough to pass legislation into law.

It is also noteworthy that this rulemaking comes at a time when litigants are more prone to forum shop for sympathetic judges. In the past, challenges against government agencies were brought in Washington, D.C., and sometimes challenges against the FDA were brought in Maryland.

Litigants are increasingly bringing challenges against the FDA in courts that have a history of issuing nationwide injunctions barring public health and safety-oriented rulemakings. In those jurisdictions, it is arguably even more important for courts to hear from a wide variety of stakeholders supporting a rule for the rulemaking to survive.

This may be the most historic rulemaking we have seen from FDA in a generation, both because of the significance of the rulemaking itself and the litigation soon to follow.

The comment period on the rule ends Dec. 4, and the FDA has been firm it will not extend the comment period, so time is running out for anyone who wants to influence the outcome. We will all be watching how quickly the FDA finalizes the rule, and what the final rule ultimately looks like.

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[1] Medical Devices; Laboratory Developed Tests, 88 Fed. Reg. 68,006 (Oct. 3, 2023) (to be codified at 21 C.F.R. pt. 809), https://www.federalregister.gov/d/2023-21662.

[2] Loper Bright Enter., Inc. v. Raimondo, 45 F.4th 359 (D.C. Cir. 2022) (cert. granted).

[3] Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837 (1984).

[4] F.C.C. v. Fox Television Stations, Inc., 566 U.S. 502 (2009).

[5] D.H.S. v. Regents of the Univ. of Cal., 140 S.Ct. 1891 (2020).

[6] See e.g. West Virginia v. E.P.A., 142 S.Ct. 2587 (2022) (Gorsuch, J., concurring); Biden v. Nebraska, 143 S.Ct. 2355 (2023) (Barrett, J., concurring).

[7] West Virginia v. E.P.A., 142 S.Ct. 2587 (2022).

[8] Biden v. Nebraska, 143 S.Ct. 2355 (2023).

[9] F.D.A. v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000).

[10] Apter v. Dep't of Health & Hum. Servs., 80 F.4th 579 (5th Cir. 2023).