Unwise and Unauthorized

FDA Regulation of Laboratory Developed Tests

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NOVEMBER 2023

The author is grateful to the Paragon team for their exceptional comments and work in review of the paper.

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EXECUTIVE SUMMARY

What this policy brief covers: The Food and Drug Administration (FDA) has proposed a rule in order to establish its long-claimed authority to regulate laboratory-developed tests (LDTs) — tests that are designed, manufactured, and used within a single laboratory — as medical devices. The FDA regulates devices under the Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (FDCA). The FDA has asserted for at least 30 years that this includes the authority to regulate LDTs as devices. But until recently, the agency, citing "enforcement discretion," has rarely regulated LDTs. LDTs have instead been regulated by the Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). This paper discusses whether FDA has the authority to regulate LDTs and whether such regulation is advisable.

Findings: The FDA likely lacks the statutory authority to regulate LDTs. LDTs are more like medical services, which the FDA may not regulate, than medical devices — manufactured, physical articles that are commercially distributed for use by third parties — which FDA can and does regulate. The FDCA makes no mention of regulating laboratories, laboratory tests, or laboratory testing services, and various sections of the statute suggest it does not apply to LDTs. Recent Supreme Court precedent makes clear that an agency may not presume it has the authority to regulate an area of significant economic activity unless Congress clearly provided that authority in the governing statute. LDTs are performed billions of times a year in thousands of laboratories generating tens of billions of dollars in revenue. FDA's proposal is likely motivated, in part, to pressure Congress to enact legislation giving the agency clear authority to regulate LDTs, such as the VALID Act.

Exempting LDTs from FDA oversight allows specialized labs the flexibility needed to rapidly create new tests for rare diseases and emergency situations. FDA regulation of LDTs could curb innovation that is particularly important in combatting emerging infectious diseases. Awaiting the development of manufactured test kits and the completion of FDA's premarket reviews could delay life-saving diagnoses and treatments. Despite FDA's claims to the contrary, the evidence is not clear that LDTs developed and used in CLIA approved high-complexity laboratories are any less reliable or accurate than FDA-approved tests. Moreover,

it is unlikely that FDA has the capacity to clear the thousands of existing LDTs along with reviewing new LDTs.

Policy suggestions: Changes to FDA's authority to regulate LDTs must come from Congress. The current system of CLIA regulation works reasonably well. Congress should resist the pressure of the FDA's proposed action and ensure that any proposal that purports to improve the regulation of LDTs actually improves public health and facilitates the development of life-saving innovation.

INTRODUCTION

The U.S. Food and Drug Administration (FDA) recently published a proposed rule that explicitly asserts its claimed authority to regulate laboratory-developed tests (LDTs) as medical devices.[1] FDA has long maintained that the Federal Food, Drug, and Cosmetic Act (FDCA) allows it to regulate LDTs, but it has almost never done so. This new move will likely both exceed the agency's statutory authority and be counterproductive, decreasing innovation in diagnostic testing and leaving the nation less prepared for the next health emergency.

The FDCA gives the FDA broad authority to regulate medical devices "intended for use in the diagnosis of disease." The agency mandates a premarket review of diagnostic test kits manufactured by one entity and sold for use in other laboratories. The FDA also claims authority to conduct premarket review of LDTs — tests that are designed, manufactured, and used within a single laboratory. Yet it has nearly always demurred, citing "enforcement discretion," and has not required the laboratories offering such tests to comply with FDA regulations that normally require medical devices to undergo premarket review and receive approval, clearance, or authorization from the agency.

LDTs though, do not escape regulation. The Clinical Laboratory Improvement Amendments of 1988 (CLIA) authorizes the Centers for Medicare and Medicaid Services (CMS) to regulate labs that perform diagnostic testing for humans. Only laboratories that are certified to perform high-complexity testing — the highest of three levels of complexity under CLIA[2] — may develop and use LDTs. Certification involves inspection by CMS, establishment of a quality assurance and proficiency testing program, and compliance with other requirements.

The FDA has long claimed it has concurrent jurisdiction to regulate LDTs. Yet the recently proposed rule marks the first time the agency has engaged in notice-and-comment rulemaking to set out the authority it has asserted for the past 31 years.

FDA'S REGULATORY PROPOSAL

FDA's proposal would "amend its regulations to make explicit that in vitro diagnostic products (IVDs) are devices" under the FDCA regardless of where they are made and used and who else regulates them, "including when the manufacturer of the IVD is a laboratory." The agency "intends to phase out its general enforcement discretion approach for laboratory developed

1 88 Fed. Reg. 68006 (Oct. 3, 2023), https://www.govinfo.gov/content/pkg/FR-2023-10-03/pdf/2023-21662.pdf.

2 42 C.F.R. § 493.5, https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493/subpart-A/section-493.5.

tests (LDTs) so that IVDs manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs."[3]

The FDA claims that the rule is needed to reaffirm the agency's authority to regulate LDTs because the nature of LDTs has changed since the Medical Device Amendments of 1976, which gave FDA the authority to regulate devices, were first enacted. According to the FDA, back then "LDTs were mostly manufactured in small volumes by laboratories that served their local communities. They were typically intended for use in diagnosing rare diseases or for other uses to meet the needs of a local patient population, or were generally similar to well-characterized, standard tests." Today, the agency claims that

> many LDTs rely on high-tech or complex instrumentation and software to generate results and clinical interpretations. They are often used in laboratories outside of the patient's healthcare setting and are often manufactured in high volume for large and diverse populations. Many LDTs are manufactured by laboratory corporations that market the tests nationwide, as they accept specimens from patients across the country and run their LDTs in very large volumes in a single laboratory.

In fact, while LDTs are commonly used in many labs, no one knows precisely how often and where they are used or for what clinical purposes.[4] And what FDA describes as a problem with modern LDTs — that labs make them available to "diverse populations" from "across the country" — is actually a useful feature. LDTs are often created in response to an unmet clinical need or where existing diagnostic tests are inadequate. LDTs were developed for emerging infectious diseases — such as HIV, SARS and H1N1 — long before FDA-approved tests were available. Similarly, high-complexity laboratories developed specialized tests for various cancer biomarkers years before FDA-approved test kits reached the general market.

The FDA cannot credibly claim that changed circumstances prompted it to issue the proposed rule. FDA has claimed that LDTs are devices subject to its authority since 1992.[5] In 2006 and 2007, FDA published draft guidance on a subset of LDTs called In Vitro Diagnostic Multivariate Index Assays, but it never finalized the guidance and instead announced its intent to regulate all LDTs in June 2010.[6] FDA issued draft guidance outlining proposed LDT regulation in 2014.[7]

3 88 Fed. Reg. 68006 (Oct. 3, 2023).

4 Pew Charitable Trusts, "The Role of Lab-Developed Tests in the In Vitro Diagnostics Market," October 2021, https://www.pewtrusts.org/-/media/assets/2021/10/understanding-the-role-of-lab-developed-tests-in-vitro-diagnostics.pdf.

5 Robert Charrow, General Counsel, Department of Health and Human Services, letter to Stephen Hahn, Commissioner of Food and Drugs, June 22, 2020, https://www.thefdalawblog.com/wp-content/uploads/2021/11/HHS-Legal-Memo-on-LDTs-by-Charrow-00864663.pdf.

6 Amanda K. Sarata, "FDA Regulation of Laboratory-Developed Tests (LDTs)," Congressional Research Service, updated December 7, 2022, https://crsreports.congress.gov/product/pdf/IF/IF11389.

7 79 Fed. Reg. 59779 (Oct. 3, 2014), https://www.federalregister.gov/documents/2014/10/03/2014-23586/food-and-drug-administration-notification-and-medical-device-reporting-for-laboratory-developed.

But the agency did not follow through and withdrew the guidance in late 2016. As will be discussed below, FDA made an ill-fated effort to regulate LDTs during the COVID-19 pandemic through guidance documents. FDA's proposed rule seems more like a response to the legal opinion on LDTs from the Department of Health and Human Services (HHS) during the pandemic that cast doubt on FDA's authority over LDTs in general and suggested that administrative efforts to assert authority over LDTs could proceed only through notice-and-comment rulemaking, not through guidance documents.[8]

CONGRESS HAS NOT AUTHORIZED THE FDA TO REGULATE LDTS

A fundamental problem with FDA's proposed rule is that Congress never clearly authorized the FDA to regulate clinical laboratory services.[9] While the FDA has long claimed authority to regulate LDTs under the FDCA, no court has ruled on the matter. The 1976 Medical Device Amendments to the FDCA do not mention laboratories, laboratory tests, or laboratory testing services.

There is no question that the FDCA gives the FDA the authority to regulate medical devices — including IVDs, which are manufactured by third parties and sold as test kits to clinical laboratories — for use in the diagnosis, prevention, cure, mitigation, or treatment of disease.[10] A diagnostic test designed for use by third parties and shipped to other laboratories might arguably justify regulatory oversight to better ensure the test's operability and reliability.

That is why FDA review of medical products, including testing devices, focuses on the device's performance regardless of where it is used. FDA is concerned with analytical validity — whether a test can accurately and reliably measure what it claims to measure — as well as clinical validity — whether a test accurately measures the presence of, or risk for, a given health condition.[11] The FDA review looks at three factors: (1) Does the product/test accurately and reproducibly measure what it is supposed to measure? (2) Does what it measures have clinical meaning — for example, correlating with a diagnosis or treatment outcome? and (3) Is the manufacturer's labeling about the test truthful and accurate?[12] The FDA can specify that

8 Charrow, letter to Hahn.

9 Barbara J. Evans and Ellen Wright Clayton, "Deadly Delay: The FDA's Role in America's COVID-Testing Debacle," *Yale Law Journal* 130 (2020-2021), https://www.yalelawjournal.org/forum/deadly-delay-the-fdas-role-in-americas-covid-testing-debacle.

10 21 U.S.C. § 321.

11 Pew Charitable Trusts, "What Are In Vitro Diagnostic Tests, and How Are They Regulated?," May 2019, https://www.pewtrusts.org/-/media/assets/2019/05/what-are-in-vitro-diagnostic-tests-and-how-are-they-regulated.pdf.

12 FDA, "Optimizing FDA's Regulatory Oversight of Next-Generation Sequencing Diagnostic Tests," February 20, 2015, https://wayback.archive-it.org/7993/20170113000324/http:/www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM439974.pdf.

the diagnostic product it approves is suitable for use only by CLIA-certified high-complexity laboratories, as opposed to laboratories certified for less complex testing under CLIA.[13]

Laboratory regulation under CLIA, in contrast, is solely concerned with analytical validity, relying on the scientific experts in the lab and the physicians who order the tests and receive the results to determine clinical validity and utility. CLIA regulations focus on the quality of services within a particular laboratory — ensuring that personnel are qualified, follow appropriate policies and procedures, work under adequate supervision and controls, and maintain proper records documenting test accuracy and reliability.[14] CLIA-regulated labs use FDA-approved devices along with instruments and components that are not legally marketed for clinical use.

LDTs Are Not Medical Devices

The hospital, academic, and state labs that typically develop LDTs, along with the American Clinical Laboratory Association, claim, with justification, that LDTs are not medical devices but rather services performed by clinical labs — a form of "medical practice" that FDA has no authority to regulate.[15] This position finds support in Medicare Part B, which pays for diagnostic laboratory tests (including LDTs) as a service rather than a discrete article of merchandise.[16]

Medical devices are manufactured, physical articles of commerce, intended for use by third parties. The FDCA defines a *device* as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory," i.e., a physical article or product.[17]

An LDT, in contrast, is a methodology or process developed in-house for use in a single laboratory to generate results for medical practitioners. It is more akin to a service that incorporates proprietary methodologies and protocols than to a physical object. The fact that laboratories use devices to render services does not turn those services into devices. Otherwise, the FDA could classify every medical or surgical procedure as a device.

13 FDA, "Administrative Procedures for CLIA Categorization," October 2, 2017, https://www.fda.gov/media/71065/download.

14 42 C.F.R. § 493.

15 American Clinical Laboratory Association, "Citizen Petition," June 4, 2013, https://www.acla.com/wp-content/uploads/2013/12/060413-Citizen-Petition-to-FDA-Regarding-Laboratory-Developed-Tests-LDTs.pdf.

16 Social Security Act, § 1861(s).

17 21 U.S.C. 321(h)(1).

LDTs Are Not Commercially Distributed

Section 510(k) of the FDCA sets out the premarket review requirement, which is the primary difference between regulation under CLIA and regulation under the FDCA. Section 510(k) requires that persons subject to it "begin the introduction or delivery for introduction into interstate commerce for *commercial distribution* of a device" [emphasis added].[18]

This statutory language suggests that, to be subject to regulation, the device would have to be supplied or distributed beyond a single laboratory. The FDA's own definition of *commercial distribution* — "any distribution of a device intended for human use which is held or offered for sale but does not include … [i]nternal or interplant transfer of a device between establishments within the same parent, subsidiary, and/or affiliate company"[19] — seems consistent with the statute's plain language and would not apply to LDTs, which are, by definition, developed and used within a single laboratory.

Furthermore, the FDA's premarket registration[20], notification and review[21] and approval requirements[22] apply only to "persons" who make a device. The FDCA states, "The term 'person' includes individual, partnership, corporation, and association."[23] This definition would likely not apply to state-owned laboratories in departments of public health or universities, which are the most common developers of LDTs. As the HHS general counsel observed in his June 2020 legal memo to FDA on LDTs, the FDCA "separately defines 'State,' '… [to] mean [] any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico.' [FDAC] § 201a. The two definitions are not linked or cross-referenced. Thus, a 'person' is not a 'State.'"[24]

Regulating LDTs Would Interfere in the Practice of Medicine

FDA regulation of LDTs may run afoul of a section of the FDCA entitled "Practice of Medicine" — "Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."[25] This language makes clear that the FDA may not regulate the practice of medicine. Physicians routinely rely on laboratory tests, including LDTs. But they primarily rely

18 21 U.S.C. §360(k).
19 21 C.F.R. §807.3.
20 FDCA §§ 510(b) and (c); 21 U.S.C. §§ 360(b)(2) and 360(c).
21 FDCA § 510(k).
22 FDCA § 515; 21 U.S.C. § 360e.
23 21 U.S.C. § 321(e).
24 Charrow, letter to Hahn.
25 21 U.S.C. § 396.

on their own knowledge to assess the clinical significance of the results. FDA's proposed regulation of LDT services as devices would "interfere with the authority of … health care practitioner[s]" to make diagnosis and treatment decisions.[26]

No Authority without Clear Statutory Language

Any assertion that FDA has the authority to regulate LDTs will have to overcome the fact that the statute is silent on this authority and contains many sections that seem to run contrary to it. As the Supreme Court made clear more than 20 years ago in *FDA v. Brown & Williamson Tobacco Corp.*[27] — where the FDA asserted the right to regulate tobacco without any statutory authority — and more recently in *West Virginia v. EPA*,[28] if an administrative agency tries to address an issue of great "economic and political significance" it "must point to 'clear congressional authorization' for the power it claims." It is estimated that 3.3 billion IVD tests are performed in the United States every year with a significant portion — as many as 50 percent — being LDTs performed in 12,000 CLIA-certified high-complexity labs.[29] While acknowledging uncertainties due to a paucity of data, FDA economists found that annual revenue estimates in the United States for LDTs range from $2.4 billion to $97 billion, with an average revenue estimate of $27 billion.[30] Courts cannot presume that Congress meant to allow FDA to regulate LDTs' significant economic activity without clear statutory language.

For decades, laboratories have openly developed LDTs that physicians ordered and used to diagnose and treat large numbers of patients. As the Supreme Court noted in a 2014 case, "When an agency claims to discover in a long-extant statute an unheralded power to regulate 'a significant portion of the American economy,' we typically greet its announcement with a measure of skepticism." (citations omitted).[31] Similarly, in a more recent case invalidating an Occupational Safety and Health Administration (OSHA) mandate that "84 million Americans … either obtain a COVID-19 vaccine or undergo weekly medical testing at their own expense," the Court found it "telling that OSHA, in its half century of existence," had never relied on its authority to regulate occupational hazards to impose such a broad measure that Congress had not clearly authorized.[32]

26 21 U.S.C. § 396.

27 529 U.S. 120, 160 (2000).

28 597 U.S.__, __, 142, S.Ct. 2587, 2609 (2022).

29 Pew Charitable Trusts, "The Role of Lab-Developed Tests;" FDA, *Laboratory Developed Tests Proposed Rule*, https://www.fda.gov/media/172557/download?attachment.

30 FDA Economics Staff, *Laboratory Developed Tests Proposed Rule*: Preliminary Regulatory Impact Analysis, Docket No. FDA-2023-N-2177. https://www.fda.gov/media/172557/download?attachment.

31 *Util. Air Regulatory Grp. v. E.P.A.* (573 U.S. 302, 324, 134 S. Ct. 2427, 2444 (2014)).

32 *National Federation of Independent Business v. Occupational Health and Safety Administration* (595 U.S __, __, 142 S.Ct. 661, 665-66 (2022)).

FDA's 16-year delay in publicly asserting authority to regulate LDTs (1976 to 1992) and its subsequent issuance (2014) and withdrawal of draft guidance establishing oversight suggest that the agency was unsure of its actual authority over LDTs. The enactment in 1988 of a distinct regulatory framework for clinical laboratory tests in CLIA, administered by CMS rather than FDA, suggests that Congress recognized that laboratory testing services and medical devices raise different regulatory issues and intended LDTs to be separately regulated by CMS under CLIA.[33] If Congress believed the FDA already had authority to regulate LDTs as devices under the 1976 Medical Device Amendments, there would have been little reason for Congress to enact the 1988 CLIA amendments. Congress's action was purposeful. While considering CLIA, Congress received written testimony from the director of the New York State Wadsworth Center for Laboratories and Research that "while FDA requirements must be met if a kit or reagent is to be commercially marketed, labs that use their own techniques and reagents need no approval."[34] And CMS's CLIA regulations clearly established performance specifications for laboratories introducing "test system[s] not subject to FDA clearance or approval (including methods developed in-house…)."[35]

In a tacit acknowledgement of FDA's questionable authority, some members of Congress proposed explicitly empowering the FDA to regulate LDTs through the Verifying Accurate, Leading-edge IVCT Development (VALID) Act. VALID would establish a new category called *in vitro* clinical tests (IVCTs) with a risk-based regulatory framework for premarket authorization along with a user fee program. It would exempt low-risk and low-volume tests such as those for rare diseases, modifications of previously approved tests, and some LDTs already in use. Proponents claim that VALID would create an approval pathway for diagnostic tests that is better suited to allow timely access to these tests than the FDA's usual device approval pathway.

VALID, first introduced in 2018, has been reintroduced several times since — including on March 5, 2020,[36] during the early days of the pandemic — but has failed to advance. While it came close to passage in 2022, it was ultimately dropped from the FY2023 Appropriations Act. Passage is unlikely in 2023.[37]

33 Paul D. Clement and Laurence H. Tribe, "Laboratory Testing Services, as the Practice of Medicine, Cannot Be Regulated as Medical Devices," American Clinical Laboratory Association, https://www.acla.com/wp-content/uploads/2015/01/Tribe-Clement-White-Paper-1-6-15.pdf.

34 Jonathan R Genzen et al., "Laboratory-Developed Tests: A Legislative and Regulatory Review," *Clinical Chemistry* 63, no. 10 (October 1, 2017): 1575-1584, https://academic.oup.com/clinchem/article/63/10/1575/5612690.

35 42 C.F.R. § 493.1253(b)(2).

36 Verifying Accurate Leading-edge IVCT [in vitro clinical test] Development (VALID) Act of 2020, H.R. 6102, 116th Cong. (2020) (companion to S. 3404, 116th Cong. (2020)).

37 Ferdous Al-Faruque, "Stakeholders Continue Push for VALID Act in Wake of FDA's Proposed LDT Rule," *Regulatory Focus*, October 6, 2023, https://www.raps.org/News-and-Articles/News-Articles/2023/10/Stakeholders-continue-push-for-VALID-Act-in-wake-o.

Both FDA commissioner Robert Califf and Elizabeth Hillbrenner, associate director for scientific and regulatory programs at FDA's Center for Devices and Radiological Health have pushed Congress to enact VALID or other legislation that would explicitly give FDA authority to regulate LDTs.[38] Both indicated that if Congress does not act, FDA would pursue the regulatory route. It seems likely that FDA's proposed rule is motivated, at least in part, to spur Congress to enact VALID or similar legislation.

Pursuing a regulatory approach without clear statutory authority as an end run around Congress would almost certainly elicit legal actions that would delay or defeat FDA's efforts. Moreover, there are good reasons to believe that the current CLIA-based regulatory structure may be the best model for ensuring both safety and innovation of LDTs. For example, VALID was defeated in late 2022 largely due to the opposition of Senate and House leaders, who argued it would place undue burdens on academic medical centers.[39]

FDA REGULATION WOULD STIFLE INNOVATION AND WORSEN PATIENT HEALTH

Exempting LDTs from FDA oversight affords these specialized labs the flexibility needed to rapidly create new tests for rare diseases and emergent situations such as COVID-19. And it allows labs to easily modify and update tests as new scientific information becomes available. In 2015, Paul Clement and Laurence Tribe presciently wrote:

> FDA oversight would also render critical testing, particularly for patients with emergent infectious diseases, unavailable in the "lag time" before FDA approval. The FDA approval process is protracted and not designed for the rapid clearance of tests. Many clinical laboratories track world trends regarding infectious diseases and have demonstrated immediate or near-immediate responses to infectious diseases ranging from SARS to H1N1 and Avian Influenza. *In these fast-moving, life-or-death situations, awaiting the development of manufactured test kits and the completion of FDA's clearance procedures could entail potentially catastrophic delays, with disastrous consequences for patient care* [emphasis added].[40]

38 Ferdous Al-Faruque, "US Lawmakers Again Propose Diagnostics Reform Bill," *Regulatory Focus*, March 30, 2023, https://www.raps.org/News-and-Articles/News-Articles/2023/3/US-lawmakers-again-propose-diagnostics-reform-bill; Mark McCarty, "Hillebrenner Says FDA No Longer Waiting on Congress for LDT Regulation," *BioWorld*, March 1, 2023, https://www.bioworld.com/articles/694701-hillebrenner-says-fda-no-longer-waiting-on-congress-for-ldt-regulation?v=preview.

39 Al-Faruque, "US Lawmakers Again Propose Diagnostics Reform Bill."

40 Clement and Tribe, "Laboratory Testing Services".

FDA's Counterproductive Regulation of LDTs During the Pandemic

Clement and Tribe's fear was realized when the COVID-19 pandemic arrived early in 2020. Several academic labs, including the University of Washington, wanted to employ tests they developed for the coronavirus responsible for COVID-19, SARS-CoV-2. But the FDA ordered them to stop.[41] In the early days of the biggest public health emergency in a century, the agency took the bizarre step of ceasing its usual exercise of enforcement discretion that previously made LDTs readily available and insisted that the tests needed FDA approval. The result was a public health fiasco.

On January 31, 2020, HHS Secretary Alex Azar declared a public health emergency.[42] The declaration triggered various FDA authorities including, under Section 564 of the FDCA, the authority to grant emergency use authorizations (EUAs) for medical products that the FDA had not yet cleared or approved as safe and effective. On February 4, Secretary Azar issued a determination that "circumstances exist justifying" EUAs for COVID-19 tests.[43]

Through guidance documents, FDA took the position that once an HHS EUA declaration is in place, laboratories should *not* use their own LDTs to diagnose the disease that triggered the emergency until they go through the EUA process. All COVID-19 tests, whether they were kits developed for commercial distribution or LDTs, would have to obtain EUAs before being used. For commercial test kits, the EUA process would expedite access to medical products during an emergency that would otherwise require premarket review. However, because FDA generally waived premarket requirements for LDTs through enforcement discretion, requiring the EUA process would impose additional regulatory requirements for developing and using an LDT in an emergency.

FDA justified this policy in a March 1, 2020, website announcement, claiming that LDTs dealing with COVID-19 "present a higher risk. This is because they are developed to diagnose serious or life-threatening diseases or conditions that not only have serious implications for individual patient care, but also for analyses of disease progression and public health decision-making."[44]

41 Brian H. Shirts, "We'll See More Shortages of Diagnostic Tests If the *FDA* Has Its Way," *STAT*, April 15, 2020, https://www.statnews.com/2020/04/15/diagnostic-tests-shortages-fda-decision/.

42 HHS, "Determination That a Public Health Emergency Exists," https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx.

43 HHS, "Determination of a Public Health Emergency and Declaration That Circumstances Exist Justifying Authorizations Pursuant to Section 564(B) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3," February 4, 2020, https://www.fda.gov/media/135010/download.

44 FDA, "Information for Laboratories Implementing IVD Tests Under EUA," March 1, 2020, https://web.archive.org/web/20200316194747/https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/information-laboratories-implementing-ivd-tests-under-eua.

Multiple academic and state and local public health laboratories had created their own COVID-19 tests. But, when the Association of Public Health Laboratories requested that the FDA commissioner use his discretion to allow these labs to use their LDTs, FDA declared that labs must submit their tests for emergency use authorizations.[45]

Unfortunately, the only EUA the FDA initially granted was for a test created by the Centers for Disease Control and Prevention (CDC). It quickly became apparent that the CDC test was flawed and unreliable, but FDA persisted with its policy of requiring EUAs that it seemed unwilling to grant. for a month. FDA's policy meant that testing was essentially unavailable for the month of February as COVID-19 spread, undetected, around the country.

The FDA relented only on February 29, when it issued a new policy[46] allowing laboratories that are certified to perform high-complexity testing under CLIA to develop and use validated COVID-19 diagnostics so long as they complete EUA requests within 15 days. Use could continue until the FDA completed review of the EUA applications. In essence, this policy was a form of enforcement discretion for LDTs for COVID-19.

On August 19, 2020, HHS further relaxed FDA oversight of LDTS, directing the agency to cease enforcing premarket review requirements for all LDTs — including COVID-19 LDTs — without first undergoing formal agency notice-and-comment rulemaking.[47] But the Biden administration — citing the need to ensure that tests are accurate and reliable — reversed this policy on November 15, 2021.[48]

FDA's initial push 31 years ago to regulate LDTs stemmed from concerns that started with the Human Genome Project in the 1990s, which uncovered many genetic variants of unknown significance.[49] Most of the available genetic tests in this period were LDTs. There were worries that analytic validity alone — accurately measuring a particular genetic variant — would not necessarily provide clinically useful information to guide diagnostic or treatment decisions in genetic testing. But this should not have been a concern during the COVID-19 pandemic, when LDTs were developed to test for the presence of the SARS-CoV-2 virus that causes the

45 Sheri Fink and Mike Baker, "'It's Just Everywhere Already': How Delays in Testing Set Back the U.S. Coronavirus Response," *New York Times*, March 16, 2021, https://www.nytimes.com/2020/03/10/us/coronavirus-testing-delays.html.

46 See FDA, "Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency: Guidance for Clinical Laboratories and Food and Drug Administration Staff," February 29, 2020, https://web.archive.org/web/20200229191633/https:/www.fda.gov/media/135659/download. This guidance was subsequently revised in March 2020, May 2020, November 2021, September 2022, and January 2023.

47 Amanda K. Sarata, "HHS Announcement on FDA Premarket Review of Laboratory-Developed Tests (LDTs)," Congressional Research Service, December 3, 2020, https://crsreports.congress.gov/product/pdf/IN/IN11548.

48 FDA, "Coronavirus (COVID-19) Update: FDA Updates Test Policies to Help to Ensure Accuracy and Reliability of Tests and Increase Access to At-Home Tests," press release, November 15, 2021, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-updates-test-policies-help-ensure-accuracy-and-reliability-tests-and.

49 Task Force on Genetic Testing, *Promoting Safe and Effective Genetic Testing in the United States*, September 1997, https://www.genome.gov/10001733/genetic-testing-report.

disease and for antibodies to that virus that would indicate prior infection. Unlike genetic tests of unclear significance, there was no question of the clinical validity of accurately measuring the presence of the virus or antibodies to it.

FDA's Flawed Justification for Regulating LDTs

In a benefit-cost analysis to justify the proposed LDT rule,[50] FDA economists cited an internal FDA analysis[51] of the first 125 EUA requests for COVID-19 molecular tests submitted by laboratories to FDA for which there was a completed or preliminary evaluation. It claims that about two-thirds of the submissions had "major issues," nearly all of which were inadequate or missing validation. It is impossible to verify this analysis, as it is an internal memorandum compiled by a single agency official. It also lacks context, because it does not report how this compares with EUA submissions from commercial test kit manufacturers. In fact, as Dr. Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health, acknowledged, "Similar problems were seen with commercial manufacturers."[52] Many of the initial validation problems resulted from the fact that FDA allowed utilization of "contrived samples" of synthetic DNA and RNA fragments for analytical verification because patient samples of viral RNA or the virus were not available.[53] In "the majority of cases" with identified validation issues, "the FDA worked with the laboratories to correct the issues and permit continued testing."[54] Finally, it bears repeating that the first EUA application that the FDA *did approve* was the flawed CDC COVID test, which clearly had major issues.

A review from the U.S. Government Accountability Office (GAO) highlighted another source of problems with validation data during the early stages of the pandemic, reporting that:

> many laboratories found it difficult to apply for an EUA for their tests because they were unfamiliar with FDA's EUA requirements and did not have the resources or internal expertise needed to navigate FDA's EUA process. FDA acknowledged that some laboratories were unfamiliar with the EUA process, and that this created misunderstandings and confusion.[55]

50 FDA, *Laboratory Developed Tests Proposed Rule*.

51 Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, Center for Devices and Radiological Health, FDA, "Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2," memorandum, September 22, 2023, https://www.regulations.gov/document/FDA-2023-N-2177-0121.

52 Jeffrey Shuren and Timothy Stenzel, "Covid-19 Molecular Diagnostic Testing — Lessons Learned," *New England Journal of Medicine*, October 22, 2020, https://www.nejm.org/doi/full/10.1056/NEJMp2023830.

53 Shuren and Stenzel, "Covid-19 Molecular Diagnostic Testing — Lessons Learned."

54 Shuren and Stenzel, "Covid-19 Molecular Diagnostic Testing — Lessons Learned."

55 GAO, "COVID-19: FDA Took Steps to Help Make Tests Available; Policy for Future Public Health Emergencies Needed," May 2022, https://www.regulations.gov/document/FDA-2023-N-2177-0111.

The FDA economists' analysis attempts to calculate the benefits of regulating LDTs, described as the reduction in "costs associated with unsafe or ineffective IVDs" offered as LDTs. The calculation is a lengthy series of estimates and assumptions where small inaccuracies can snowball into major errors.

Perhaps the most glaring problem with FDA's analysis was its reliance on a single small study of oncology LDTs that reported that 47 percent of laboratories using LDTs misidentified some of the variants as compared with an FDA-approved test.[56] In calculating fatalities associated with a preventable misdiagnosis, the FDA economists cited this study as if 47 percent of LDTs would result in a misdiagnosis. But this was a gross overestimate. Among these labs with errors, nearly all correctly identified more than three quarters of the variants representing 56 types of mutations. In other words, even laboratories that reported some errors would get the correct result most of the time. Moreover, not every failure to correctly identify a variant would result in a treatment error. The study authors acknowledged "that the potential clinical significance of variant identification errors was not evaluated."

The FDA economists also ignored literature showing that LDTs for oncology testing were highly accurate and produced comparable or superior results compared with commercially available, FDA-cleared tests.[57] In addition, the FDA study extrapolates results from one oncology study to LDTs for all types of diseases. The large number of genetic variants in cancers relative to variants in other types of analytes (such as infectious agents) makes it likely that FDA's generalization overstates error rates in other LDTs.

Suppressing Innovation and Decreasing Competition

FDA's cost-benefit analysis acknowledges that the rule will impose significant compliance costs on laboratories that offer LDTs — $35.5 billion over the multiyear phase-in and additional recurring costs of $4.2 billion. The analysis concedes that this may lead some laboratories to exit the market or discontinue certain LDTs they offer.[58]

The FDA analysis reports that 90 percent of the laboratories that make LDTs are considered by the Small Business Administration to be small business (annual receipts of less than $41.5

56 John D. Pfeifer et al., "Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics," *American Journal of Clinical Pathology* 157, no. 4 (April 2022): 628-638, https://academic.oup.com/ajcp/article/157/4/628/6454342.

57 Annette S. Kim et al., "Comparison of Laboratory-Developed Tests and FDA-Approved Assays for *BRAF*, *EGFR*, and *KRAS* Testing," *JAMA Oncology* 4, no. 6 (June 2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6145687/; Joel T. Moncur et al., "Performance Comparison of Different Analytic Methods in Proficiency Testing for Mutations in the *BRAF*, *EGFR*, and *KRAS* Genes: A Study of the College of American Pathologists Molecular Oncology Committee," *Archives of Pathology and Laboratory Medicine* 143, no. 10 (October 2019): 1203-1211, https://pubmed.ncbi.nlm.nih.gov/30969158/; Wanlong Ma et al., "Significant Improvement in Detecting BRAF, KRAS, and EGFR Mutations Using Next-Generation Sequencing as Compared with FDA-Cleared Kits," *Molecular Diagnosis and Therapy* 5, no. 21 (October 2017): 571-579, https://pubmed.ncbi.nlm.nih.gov/28639239/.

58 FDA, *Laboratory Developed Tests Proposed Rule*.

million) and that they manufacture 46 percent of IVDs offered as LDTs. Under the new rule, these small laboratories would have annualized costs per entity that are 22.9 percent of receipts, "making it likely that some small entities in this size category would exit the market or reduce operations as the burden is significant."[59] And small laboratories are far more likely to reduce operations or exit the market than are large laboratories whose costs are a far lower percentage of revenues.

Society would lose the benefit of innovation in testing that these smaller labs bring to the market. Yet the FDA made no attempt to estimate the economic and health costs associated with the decreased number of tests available for rare diseases or diseases for which no FDA-approved tests are available. At a minimum, instituting FDA review would impose significant lags in availability of testing, which could be particularly harmful in emergencies such as a new pandemic. As was apparent during the COVID-19 pandemic, delays in testing lead to health and economic costs.

FDA also did not estimate the costs of decreased innovation and decreased test performance of FDA-approved tests. The majority of labs routinely modify FDA-approved tests to improve performance or reflect local populations and conditions, thereby rendering the tests as LDTs, which would need FDA review.[60] Labs would be loath to improve approved tests if it means incurring large administrative compliance costs.

If larger laboratories take over production of certain IVDs currently offered as LDTs by smaller labs, market concentration will increase, leading to higher prices and reduced consumer access. If no one picks up the discontinued tests, patients will lose access to valuable tests for unmet clinical needs or where available tests are inadequate. And if the prospect of a lengthy and costly FDA process discourages labs from creating new tests or tweaking FDA approved tests to make them better, patients will suffer.

Can FDA Handle the Increased Workload?

The new regulation would require FDA to perform premarket review for existing and new LDTs and make clearance, authorization, or approval determinations. It is unlikely that FDA can handle the additional administrative burden. GAO found that by September 30, 2021, FDA had granted EUAs for 412 COVID-19 tests, but there were 370 tests — 285 LDTs and 85 tests developed by commercial manufacturers — for which FDA had received EUA requests but had not reviewed to make an EUA determination. Regular FDA review processes are more extensive than the EUA reviews that FDA had so much trouble carrying out.

59 FDA, *Laboratory Developed Tests Proposed Rule*.

60 Kim et al., "Comparison of Laboratory-Developed Tests and FDA-Approved Assays for *BRAF*, *EGFR*, and *KRAS* Testing."

FDA economists estimate it will cost nearly $3.5 billion for the agency to review existing LDTs and that there will be significant ongoing expenditures to review new LDTs.[61] Under the proposed rule laboratories would pay fees to FDA for establishment registration, premarket submissions (where applicable), and periodic reporting for IVDs with an approved PMA. But these revenue transfers to FDA would not completely offset FDA's costs. How the agency would fund these reviews is unclear.

CONCLUSION

LDTs and the sophisticated laboratories that develop and use them are an important source of innovation in testing for rare diseases and in emergency situations. The COVID-19 experience demonstrates that excess regulation of LDTs can have deadly consequences. It also demonstrates what happens when the FDA tries to supplant physicians' role as medical practitioners in determining whether and how to use analytically valid tests in treating patients.

FDA's proposed rule is ill-advised and likely exceeds the agency's statutory authority. Adding costly and unnecessary regulations would suppress innovation of diagnostics when a flexible system, able to rapidly respond to emergencies, is needed. Any change to FDA's long-time, default practice of enforcement discretion should come from Congress, which will have to ensure that any proposal that purports to improve the regulation of LDTs actually improves public health and facilitates the development of life-saving innovation.

61 FDA, *Laboratory Developed Tests Proposed Rule.*