CENTER FOR
Science IN THE
Public Interest
The nonprofit publisher of Nutrition Action

December 4, 2023

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Comment on Proposed Rule re: Medical Devices; Laboratory Developed Tests (Docket No. FDA-2023-N-2177)

The undersigned individuals appreciate FDA's efforts to regulate laboratory-developed tests (LDTs) with the proposed rule titled *Medical Devices; Laboratory Developed Tests.* This proposed rule addresses a complicated and important issue by providing a straightforward solution. In sum, the proposed rule makes explicit that all in vitro diagnostic tests (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act), including when the manufacturer is a laboratory. It also proposes a policy to phase out its current enforcement discretion approach for LDTs, meaning that LDTs would generally fall under the same risk-based enforcement approach as other diagnostic tests. FDA regulation of LDTs will ensure that patients and doctors are getting results that are accurate and clinically meaningful.

LDTs are a type of IVD developed and used in a single laboratory, distinguishing them from other IVDs that are used by multiple laboratories and conventionally manufactured as medical devices.[1] LDTs are "send out" tests, meaning a sample is collected in one facility and sent to another to be tested, instead of collecting and testing a sample in the same facility.[2] Reliable LDTs are crucial, as inaccurate tests can lead, on the one hand, to failure to diagnose critical diseases or conditions (false negatives) and, on the other, to inappropriate treatment for diseases or conditions patients do not have (false positives).

The FDA has the clear authority to regulate LDTs under the 1976 Medical Device

[1] U.S. Food and Drug Administration. *The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies*. 2015. https://www.nila-usa.org/images/nila/The%20Public%20Health%20Case%20for%20FDA%20Oversight%20of%20LDTs%20110915(2)_508ed%20(1).pdf.

[2] National Academies of Sciences, Engineering, and Medicine. *Challenges and Opportunities for Precision and Personalized Nutrition: Proceedings of a Workshop*. 2022. https://nap.nationalacademies.org/catalog/26299/challenges-and-opportunities-for-precision-and-personalized-nutrition-proceedings-of.

Amendments to the FD&C Act.[3,4] As stated in the proposed rule, "the definition of "device" in the FD&C Act encompasses test systems regardless of where or by whom they are manufactured" (p. 68018). The rule goes on to say that "the FD&C Act confers jurisdiction on FDA to regulate test systems, a point that has been codified in FDA's regulations for more than half a century. And nothing in the text, history, or purpose of the statute suggests that test systems manufactured by laboratories are excluded from that jurisdiction. This interpretation is not only the most straightforward reading of the statute, it is also the most reasonable: any other interpretation would create a bifurcated scheme in which systems that are functionally identical are treated differently under the law" (p. 68019).

In the past, the agency has chosen not to use this authority, primarily because early tests were fairly simple and used on a small number of patients.[5] As a result of this lack of regulation, FDA does not even know how many tests are currently on the market,[6] but they have clearly increased in number dramatically since 1976.

Absent oversight by FDA, laboratories performing clinical tests are regulated by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA).[7,8] Industry has argued that CLIA regulation is sufficient to ensure the accuracy of LDTs. However, this framework offers weaker review standards than those required by FDA, because CMS requires only that laboratories have documentation of their tests' ability to reliably detect a biomarker (analytical validity) but does not require an assessment of the implications of those results in actual patients (clinical validity).[9] CMS also allows laboratories to design and perform their own studies to determine analytical validity and doesn't review their methodology.

In addition, CMS oversight is weaker than FDA oversight. The College of American Pathologists (CAP) and The Joint Commission (JC) are accrediting organizations under CLIA that together inspect over 8,000 laboratories.[10,11] However, inspection takes place every

---

[3] U.S. Food and Drug Administration. *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*. 2014. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/framework-regulatory-oversight-laboratory-developed-tests-ldts.

[4] Medical Device Amendments of 1976. P.L. 94-295.

[5] The PEW Charitable Trusts. *What are In Vitro Diagnostic Tests, and How are They Regulated? Oversight May Not be Keeping Pace with Changes in the Diagnostics Market*. 2019. https://www.pewtrusts.org/-/media/assets/2019/05/what-are-in-vitro-diagnostic-tests-and-how-are-they-regulated.pdf. Accessed October 10, 2023.

[6] The PEW Charitable Trusts, 2019.

[7] The PEW Charitable Trusts, 2019.

[8] Clinical Laboratory Improvement Amendments of 1988. P.L. 100-578.

[9] U.S. Centers for Medicare and Medicaid Services. *CLIA Overview*. 2013. https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ldt-and-clia_faqs.pdf

[10] American Association for Clinical Chemistry. Modernization of CLIA: LDTs. https://www.aacc.org/-/media/Files/Health-and-Science-Policy/Position-Statements/2021/AACC-Position--Modernization-of-CLIA--LDTs-update-2021.pdf?la=en&hash=FA5003C68E6B063D0767F0BCED9F7B13DEFFFE34. Accessed October 11, 2023.

[11] U.S. Centers for Medicare and Medicaid Services. Number of CLIA Certificate of Accreditation Laboratories by Accreditation Organization. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/statacrd.pdf. Accessed October 13, 2023.

two years[12] and CAP and JC only inspect on-site,[13,14] so any determination of analytical or clinical validity of tests competes with many other items that are reviewed during the on-site visit. CMS also does not regulate certain manufacturing activities such as design controls and acceptance activities, and does not require reporting of adverse events.

Even CMS agrees that FDA has the authority to regulate LDTs,[15] and oversight under FDA would be much more comprehensive. It would require high-risk tests to be individually reviewed by the agency, drawing on the agency's demonstrated expertise in device review and quality assurance, and would include review of both analytical and clinical validity for the riskiest tests.[16] FDA would also oversee manufacturer claims, labeling, and adverse event reporting, all of which are outside the bounds of CMS's authority.[17,18]

Over a decade has elapsed since FDA first proposed regulating LDTs,[19] which resulted in a 2014 draft guidance that was never finalized due to pressure from industry and Congress.[20,21] In 2015, the FDA published a report presenting 20 case studies of problematic LDTs.[22] Some test results reviewed in the report informed patients that they had diseases they did not have, leading to expensive, stressful, and potentially dangerous overtreatment. Others failed to diagnose existing disease, resulting in delay or failure to administer effective treatments until it was too late. The report also estimated the cost to society of some inaccurate tests. For example, every false-positive Lyme disease test reviewed in the report resulted in $1,226 in unnecessary treatment costs and every false-positive ovarian cancer test led to $12,578 in such costs. On the other hand, every false-negative result for breast cancer cost $775,278 in lifespan lost (about three life-years). These costs do not account for the emotional cost of inaccurate test results.

Since the FDA's report in 2015, many more LDTs have been developed and used on large numbers of patients without FDA oversight. Some of these tests include COVID-19 diagnostic tests,[23] genetic non-invasive prenatal screening tests,[24] and blood tests

---

[12] The PEW Charitable Trusts, 2021.
[13] College of American Pathologists. Laboratory Accreditation Program. https://www.cap.org/laboratory-improvement/accreditation/laboratory-accreditation-program. Accessed October 13, 2023.
[14] The Joint Commission. Laboratory Accreditation. https://www.jointcommission.org/resources/news-and-multimedia/fact-sheets/facts-about-laboratory-accreditation/. Accessed October 13, 2023.
[15] U.S. Centers for Medicare and Medicaid Services, 2013.
[16] The PEW Charitable Trusts, 2019.
[17] Medical Device Amendments of 1976. P.L. 94-295.
[18] Clinical Laboratory Improvement Amendments of 1988. P.L. 100-578.
[19] U.S. Food and Drug Administration. FDA/CDRH Public Meeting: Oversight of Laboratory Developed Tests (LDTs), Date July 19-20, 2010. https://web.archive.org/web/20110101182031/http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm. Accessed November 27, 2023.
[20] U.S. Food and Drug Administration, 2014.
[21] Genzen JR, Mohlman JS, Lynch JL, et al. Laboratory-Developed Tests: A Legislative and Regulatory Review. *Clin Chem*. 2017;63(10):1575-1584.
[22] U.S. Food and Drug Administration, 2015.
[23] Shuren J, Stenzel T. Covid-19 Molecular Diagnostic Testing – Lessons Learned. *N Engl J Med*. 2020;383(17):e97(1)-e97(3).
[24] U.S. Food and Drug Administration. *Genetic Non-Invasive Prenatal Screening Tests May Have False Results: FDA Safety Communication*. 2022. https://www.fda.gov/medical-devices/safety-communications/genetic-

manufactured by the notorious biotech company Theranos,[25] many of which have been documented to produce dangerously inaccurate results.

Recent experience with another LDT illustrates the chasm between potential FDA and actual CMS regulation. AvertD is an LDT that uses single nucleotide polymorphisms to predict whether someone with acute pain is likely to become addicted to opioids.[26] Accuracy in such a test is imperative as false negatives could lead to inappropriate opioid treatment, on the assumption that addiction is unlikely, whereas false positives may contribute to the undertreatment of pain. The company was first denied de novo marketing authorization in August 2021[27] but nevertheless introduced AvertD into the market shortly after,[28] taking advantage of FDA's enforcement discretion policy for LDTs. The company then reapplied in June 2022. In October 2022, an FDA advisory committee voted 11-2 against clearing the device because it was concerned about the clinical validity of the test and did not believe the test's benefits outweighed its risks, considering available alternative methods for assessing opioid addiction risk.[29] Thirteen months after the advisory committee meeting, the device remains uncleared by FDA but on the market, presumably regulated only under CLIA.[30]

In October of this year, CSPI filed a lawsuit against EpicGenetics in Superior Court of the District of Columbia over false and misleading claims made for its tests for fibromyalgia and a condition the company calls "Immune Deficiency Disease" (IDD).[31] EpicGenetics, a CLIA-certified and CAP-accredited company,[32] claims that its FM/a Test for fibromyalgia is "99 percent accurate" when a study conducted by the company itself found that the test produced false negative results 7% of the time and false positives almost one-third of the time in patients with rheumatoid arthritis or lupus. Its test for IDD appears to be identical to the FM/a Test for fibromyalgia, but is named the 100Sure Test. This test is marketed as "100% accurate" in diagnosing IDD, a disease that is not medically recognized. The claim is only true to the extent that the company defines IDD as being characterized exclusively by a positive FM/a test.

The proposed rule provides additional examples of patient harm resulting from inaccurate

---

non-invasive-prenatal-screening-tests-may-have-false-results-fda-safety-communication. Accessed October 15, 2023.

[25] Richardson L. *The Theranos Problem Congress Must Still Solve – Patients Need Protection*. The PEW Charitable Trusts. 2022. https://www.pewtrusts.org/en/about/news-room/opinion/2022/01/12/the-theranos-problem-congress-must-still-solve-patients-need-protection. Accessed October 15, 2023.

[26] George, J. *Thumbs Down for Genetic Test for Opioid Use Disorder, FDA Advisors Say*. MedPage Today. 2022. https://www.medpagetoday.com/painmanagement/opioids/101359. Accessed October 16, 2023.

[27] George, 2022.

[28] SOLVD Health. SOLVD Health Launces Genetic Risk Assessment for Opioid Use Disorder. https://solvdhealth.com/news-solvd-health-launches-genetic-risk-assessment-for-opioid-use-disorder/. Accessed October 20, 2023.

[29] George, 2022.

[30] AvertD. Assess Genetic Risk for Opioid Addiction with AvertD. https://avertdtest.com/home/. Accessed October 25, 2023.

[31] Center for Science in the Public Interest. CSPI Sues EpicGenetics, Maker of Test for Fibromyalgia, for False and Misleading Claims. 2023. https://www.cspinet.org/press-release/cspi-sues-epicgenetics-maker-test-fibromyalgia-false-and-misleading-claims. Accessed October 25, 2023.

[32] EpicGenetics. FM/a. https://www.fmtest.com/. Accessed October 25, 2023.

LDTs. These include:

- A genetic test for a heart signaling disorder that led to implanting an unnecessary defibrillator that delivered inappropriate shocks, posing the risk of sudden cardiac death
- A BRCA (tumor suppressor gene) test that had several false negatives, likely leading to disease progression, delay in treatment, and emotional distress, until the breast cancer diagnosis was confirmed
- A breast cancer test with false positives that led to invasive follow-up procedures, emotional distress, and unnecessary expenses.

The lack of oversight of LDTs has come to Congressional attention, but Congress has repeatedly failed to pass legislation that would establish a regulatory framework for these tests,[33,34] despite support from at least one industry trade group[35] representing mostly smaller LDT manufacturers. In the absence of legislative action in this critical area, FDA has understandably proceeded with this regulation.

FDA's proposed rule has several strengths, discussed in detail below.

1. The proposed rule in effect dispenses with the distinction between LDTs and other IVDs

FDA regulation of IVDs has in effect relied for decades upon an increasingly hard-to-justify distinction between LDTs and other IVDs. This distinction does not appear in the Medical Device Amendments,[36] but rather was a pragmatic decision made by FDA shortly after the amendments passed. That decision was based on a view of the IVD market that is increasingly antiquated as LDTs have grown in number and complexity and manufacturers have grown in size and sophistication.

2. The proposed rule contemplates a gradual, risk-based phase-out of enforcement discretion

CSPI agrees with FDA's proposed gradual, risk-based phase-out of its general enforcement discretion approach. The timeline proposed by the agency will give the industry adequate time to come into compliance with FDA's device requirements while allowing FDA to gather information on the LDT market and prioritize review of high-risk tests.

Under FDA's existing rules for IVDs and other medical devices, there are several pathways

---

[33] Congressional Research Service. *FDA Regulation of Laboratory-Developed Tests (LDTs)*. 2022. https://crsreports.congress.gov/product/pdf/IF/IF11389. Accessed October 25, 2023.
[34] Okun, E. *Politico Playbook PM: What You Missed in the Omnibus*. Politico. 2022. https://www.politico.com/newsletters/playbook-pm/2022/12/20/what-you-missed-in-the-omnibus-00074796. Accessed October 27, 2023.
[35] Advanced Medical Technology Association. *AdvaMed Statement on Introduction of Bipartisan VALID Act*. 2023. https://www.advamed.org/industry-updates/news/advamed-statement-on-introduction-of-bipartisan-valid-act/. Accessed October 30, 2023.
[36] Genzen, 2017.

to market, which vary in complexity based on the risk presented by the device.[37] These rules classify devices into class I, II, and III, with class III representing the highest risk. Under this framework, class II and III devices generally require review prior to marketing. Class II devices are usually cleared as substantially equivalent to a predicate device already on the market through the 510(k) (premarket notification) process or authorized through the de novo authorization process. Class III devices must submit a premarket approval application (PMA) that includes scientifically valid evidence establishing safety and efficacy of the device. Class I devices are exempt from premarket review. FDA has estimated that approximately 50% of IVDs offered as LDTs would not require premarket review (either through a PMA or a 510(k)) based on their risk profile.

The first regulatory element to go into effect will be the requirement to report to FDA, beginning one year after the rule is finalized, adverse events and information about when a manufacturer has initiated a correction or removal of a device to reduce a health risk. This will enable FDA to quickly identify potentially harmful LDTs with safety or performance issues. To comply with CLIA regulations, laboratories should already have systems for detecting problems with their tests, so this timeline is appropriate.

Two years after FDA publishes its final policy, laboratories must comply with registration and listing requirements, labeling requirements, and investigational use requirements. Compliance with these requirements will provide FDA with a better understanding of the LDT market to facilitate pre- and postmarket review. Requiring compliance with registration and listing requirements would enable FDA to track LDTs on the market. It would allow the agency to respond to those that raise concerns, ensure that these tests are reliable, and improve the availability of information on LDTs for healthcare providers and the public.

Three years after FDA publishes its final policy, laboratories will be required to comply with the device current good manufacturing practice and quality system (QS) requirements, which are critical to ensuring the analytical and clinical validity of tests. While FDA will leverage CLIA requirements for some QS requirements, FDA will also enforce requirements not mandated by CLIA, including design and purchasing controls, acceptance activities, corrective and preventative actions, and records requirements.

The final two phases include premarket review requirements. This review would be required for high-risk tests three and a half years after FDA publishes its final policy (not before October 1, 2027). Lastly, moderate and low-risk tests may require a premarket submission to determine if they should be cleared or offered de novo classification. This would occur four years after FDA publishes its policy (not before April 1, 2028). This will allow the agency to prioritize review of high-risk LDTs and align premarket review with the beginning of a new user fee cycle.

3. The proposed rule includes no blanket exemption for LDTs currently on the market, low-risk tests, or those for rare diseases

[37] U.S. Food and Drug Administration. Overview of Device Regulation. https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/overview-device-regulation. Accessed November 1, 2023.

CSPI supports the enforcement of regulatory requirements for LDTs that are currently on the market, low-risk tests, and those for rare diseases. According to the proposed rule, although FDA supported less oversight of these tests in the past, it has gathered information in recent years suggesting that these categories of tests should be regulated similarly to other tests regulated by the agency. Presumably, FDA will decide which tests would be subject to regulation, using the risk-based prioritization for review as devices, as described above.

FDA justifies the inclusion of such tests in the proposed rule by stating that it has obtained information showing that "there is a high variability in the performance of IVDs offered as LDTs that are currently on the market, including in circumstances where the test technology is relatively simple and well-understood, where the tests are for rare diseases, and where the tests are low risk" (p. 68023). The proposed rule provides multiple examples of adverse event reports associated with unreliable tests submitted to FDA, articles written by investigative journalists, and peer-reviewed medical journal articles. For example, one adverse event report identified a blood test for lung cancer with a sensitivity of merely 60%.

Even if many of these tests are intended for lower-risk uses, it is necessary that they be considered within the overall framework so that FDA can keep track of this category of LDTs, ensure they are appropriately classified and risk-stratified, monitor adverse events, and adequately plan for inspections to ensure appropriate controls are being followed.

4. The proposed rule does not exempt Academic Medical Centers (AMCs) and certain other categories from regulation

CSPI supports enforcing regulatory requirements for LDTs manufactured and used at AMCs. AMCs, which typically develop such tests, have been some of the most vociferous opponents of FDA regulation.[38] AMCs may oppose regulation partly because commercialized technologies with intellectual property patents provide additional revenue.[39]

The proposed rule provides an example of an inaccurate test developed by an AMC, which underscores the need to regulate AMC-developed LDTs. The laboratory validated its COVID-19 diagnostic test with 12 positive samples that showed perfect performance. However, when FDA requested evaluation of 12 additional samples, the test only identified five of the 12 additional known positive samples as positive for a net positivity rate of only 71%. The Emergency Use Authorization (EUA) for this LDT was subsequently withdrawn.

CSPI is concerned about a possible carveout for AMCs in the final rule. All LDTs, regardless of the organization that creates them, should be held to the same regulatory standard, as an inaccurate test is a problem regardless of who produces it. A patient misdiagnosed by an

[38] The PEW Charitable Trusts, 2021.

[39] Brown M, et al. *Innovative Revenue Streams for Academic Medical Centers– Reaching Beyond Patient Care: Part Two*. American Health Law Association. 2022. https://www.pyapc.com/wp-content/uploads/2022/08/AHLA_AMCTH_Briefing_7-25-22_Brown_Cent_Beane_Vernaglia.pdf.

LDT will find little consolation in learning that it was manufactured by an AMC.

FDA has also asked for comments on whether there is a public health rationale for a longer phaseout period for laboratories with annual receipts below a certain threshold. LDTs offered by such laboratories should not be allowed a longer phaseout period. The timeframe for the phaseout provided by FDA should be adequate for all laboratories, regardless of their size.

FDA has also asked about continuing its enforcement discretion approach for LDTs where existing programs can be leveraged. Outside programs like the New York State Department of Health's Clinical Laboratory Evaluation Program are valuable but should not replace FDA review of LDTs. FDA can coordinate with these programs to gather information, such as lists of devices, but these authorities are unable to devote the personnel, nor do they have the expertise to fully regulate these products in the way that FDA does. The NYS program has approved over 10,000 LDTs, mostly from laboratories that market their LDTs nationwide.[40] While the Wadsworth Center, the designated laboratory that reviews LDTs for the NYS program, has stated that it is able to manage LDT regulation in New York State[41] (it has an obvious economic incentive for making this claim), it will likely be unable to handle the countless additional tests offered locally to patients across the country.

Conclusion

The proposed rule is designed to protect public health and is critical to ensuring that all medical devices are accurate. It presents a strong case for the need for LDT regulation and FDA's authority to regulate these tests. Further, the agency's economic analysis of impacts demonstrates that the benefits of FDA regulation outweigh the costs. We anticipate that the agency will provide additional detail in forthcoming guidance. Together, these will close one of the largest gaps in FDA oversight of medical products.

While we welcome FDA's extending its regulatory reach to LDTs, we are concerned that the rule creates additional, unfunded duties for FDA. The agency should be provided adequate funding to carry out the activities proposed in the rule ideally through appropriations or, in the alternative, through user fees. We are also concerned about the potential use of FDA's Third Party review program by LDT manufacturers. Through this program, companies select and pay vendors for device review, creating an obvious conflict of interest.

This rule is an important step towards ensuring the accuracy of LDTs that will require prioritization of regulatory actions in the absence of resources. We look forward to reviewing future FDA guidance that will describe in more detail how the agency will prioritize regulation and classify devices. We appreciate your work on this proposed rule and thank you for taking our concerns into consideration.

---

[40] Bonislawski, A. *NY State Database Offers Glimpse into Laboratory-Developed Testing Landscape.* 360Dx. 2023. https://www.360dx.com/clinical-lab-management/ny-state-database-offers-glimpse-laboratory-developed-testing-landscape. Accessed November 7, 2023.

[41] Schneider, E. LDT Review: The New York Experience. Oral presentation at: Association of Public Health Laboratories Annual Conference. May, 2015; Indianapolis, IN.

Stephanie Rogus, PhD, RDN
Campaign Manager, Scientific Integrity
Center for Science in the Public Interest
srogus@cspinet.org

Peter Lurie, MD, MPH
President and Executive Director
Center for Science in the Public Interest
plurie@cspinet.org

Angie Bakke, MBA
Executive Director
Doctors for America
Angie.Bakke@drsforamerica.org

Cara Tenenbaum, JD/MBA
Principal
Strathmore Health
cara@strathmorehealth.com

Eleanor Garrow-Holding
President and CEO
Food Allergy & Anaphylaxis Connection Team (FAACT)
eleanor.garrow@foodallergyawareness.org

Ellyn Kodroff
Founder and President
CURED (Campaign Urging Research for Eosinophilic Diseases)
ellyn@curedfoundation.org

Lisa McGiffert
President
Patient Safety Action Network
lmcgpsan@gmail.com

Thomas Silvera, MSHS-PH, CST
Co-Founder and Vice President
Elijah-Alavi Foundation
tsilvera@elijahalavifoundation.org

The TMJ Association, Ltd.