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

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The Honorable Richard Revesz
Administrator
Office of Information and Regulatory Affairs
Office of Management and Budget
725 17th Street, NW
Washington, DC 20503

Dear Administrator Revesz,

We, the undersigned organizations, are writing in support of the Food and Drug Administration (FDA) regulation of laboratory developed tests (LDTs) to ensure that patients and doctors are getting results that are accurate and clinically meaningful. LDTs have become increasingly important in clinical practice but put patients at risk and increase healthcare costs when they are inaccurate or are not supported by scientific evidence.[1] Almost a decade has elapsed since FDA first proposed regulating LDTs in a draft guidance that was never finalized due to pressure from industry and Congress.[2,3] Congress has repeatedly failed to pass legislation that would establish a regulatory framework for these tests,[4,5,6] despite support from at least one industry trade group that represents many smaller LDT manufacturers.[7] For this reason, FDA has proceeded with regulation.

FDA has the authority to regulate LDTs under the Federal Food, Drug, and Cosmetic Act (FD&C Act),[3,8] but in the past the agency has chosen not to use its authority, primarily because early tests were fairly simple and used on a small number of patients.[9] As a result of this lack of regulation, FDA does not even know about many tests that are currently on the market.[9] Pew Charitable Trusts estimates that almost 5% of the approximately 267,000 laboratories in the U.S. offer LDTs.[10]

Over time, LDTs have grown in number and complexity and many have been found to be inaccurate. In 2015, the FDA published a report presenting 20 case studies of problematic LDTs.[11] Some test results informed patients that they had diseases they did not have, leading to expensive, stressful, and potentially dangerous overtreatment.[11] Others failed to diagnose existing disease, resulting in delay or failure to administer treatments until it was too late.[11] The report also estimated the cost to society of some inaccurate tests. For example, every false-positive Lyme disease test resulted in $1,226 in unnecessary treatment costs and every false-positive ovarian cancer test led to $12,578 in unnecessary treatment costs.[11] On the other hand, every false-negative result for breast cancer cost $775,278 in lifespan lost (about three life-years).[11] And 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,[12] genetic non-invasive prenatal screening tests,[13] and Theranos blood tests,[14] many of which have been documented to produce dangerously inaccurate results.

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).[9,15] CMS requires laboratories to have documentation of their tests' ability to reliably detect a biomarker (analytical validity) but does not require documentation of the implications of those results in actual patients (clinical validity).[9,15] The College of American Pathologists (CAP) and The Joint Commission (JC) are accrediting organizations under CLIA that together inspect over 8,000 laboratories.[16,17] However, CAP and JC only inspect on-site,[18,19] so any determination of analytical or clinical validity of tests competes with many other items that are reviewed during the on-site visit. Oversight under FDA would be much more comprehensive and would include review of performance characteristics and clinical validity for the riskiest tests.[9] FDA would also oversee manufacturer claims, labeling, and adverse event reporting, which CMS does not have the authority to do.[8,15]

The regulatory experience with the marketed genetic test AvertD exemplifies the difference between FDA and CMS regulation. In 2022, an FDA advisory committee voted 11-2 against the device, which seeks to predict whether someone with acute pain would become addicted to opioids.[20] The committee was concerned about the clinical validity of the test and did not believe the test's benefits outweighed its risks considering available alternative ways of detecting opioid addiction risk. Ultimately, the FDA did not grant the test clearance. However, the test remains on the market, presumably regulated under CLIA,[21] and the false negatives may be contributing to inappropriate opioid treatment whereas the false positives may be contributing to the undertreatment of pain.

We therefore support efforts by the FDA to regulate LDTs because regulation by CMS is insufficient to protect consumers and public health, and a modern regulatory framework will improve patient access to reliable tests. Without knowledge of the content of the proposed rule, we cannot comment on the specific proposals, but we would like to take this opportunity to share our general thoughts on elements of an effective regulatory framework for these products.

Risk-Based Approach

A regulatory framework for LDTs must be risk-based so that high-risk tests – those where an undetected inaccurate result is likely to result in serious harm or death – are subject to the most stringent scrutiny by FDA. Moderate-risk tests would undergo a review of their proposed labeling and data demonstrating that tests are safe and effective, and low-risk tests would not undergo review. Risk categories and standards need to be explicit and without line-drawing that could result in few tests being classified as high-risk.

Exemptions

Exemptions from review by FDA should be narrowly tailored so that critical categories are not excluded. All tests currently on the market, especially those classified as high-risk,

should not automatically be granted exemption from review and FDA should retain the ability to review currently marketed devices should concerns arise.

No Exemptions for Academic Medical Centers (AMCs)
AMCs that develop LDTs have been strong opponents of FDA regulation of these tests because these tests have become profit centers for these institutions. However, there is no clinical justification for granting AMC-produced devices exemption from FDA review. All LDTs, regardless of where they are developed and manufactured, should be held to the same risk-based regulatory approach because from the patient perspective, inaccurate tests are harmful regardless of who produces them.

Postmarket Surveillance
FDA should have access to all manufacturing facilities and the authority to require postmarket surveillance for any test when the agency determines that review is necessary to protect public health. For select tests, this could involve providing data supporting the test's analytical or clinical validity. Manufacturers of all LDTs should be required to report all adverse events associated with the use of their test.

Transparency
The current LDT market is so opaque that even the agency charged with regulating it (much less the public) has little idea what is on the market, what basis test developers might have for their claims, and what are the tests' performance characteristics. Previous proposals have included some version of a database containing cleared/approved products, access to which would allow both FDA and the public to have knowledge of the tests offered and certain performance characteristics. This would allow the people who order and pay for tests to spend money wisely and ensures that they are getting accurate results needed to make well-informed medical decisions.

Leveraging CLIA & Other Existing Programs
Other regulatory regimens, including CMS laboratory inspections and the New York State device approval process, should be leveraged to the extent possible. Not only would that comport with FDA's least burdensome principles, but it is the most efficient way to protect public health.

Severability
The agency should consider whether parts of the rule can be separated by a severability clause. Organizations opposed to FDA regulation of LDTs through the rulemaking process are likely to challenge the rule in court. In the event the court strikes down part of the rule, a severability and survival clause could allow other parts of the rule to continue to be enforced.

FDA should use its existing authority to its full extent to protect public health. We welcome the opportunity to discuss this with you further and look forward to future engagement on this issue. Please contact Stephanie Rogus at srogus@cspinet.org with any questions.

Sincerely,

Breast Cancer Action
Breast Implant Safety Alliance (BISA)
Center for Science in the Public Interest
CURED NFP (Campaign Urging Research for Eosinophilic Diseases)
Doctors for America
Elijah-Alavi Foundation
FARE (Food Allergy Research and Education)
International FPIES Association (IFPIES)
MRSA Survivors Network
National Center for Health Research
National Women's Health Network
Our Bodies Ourselves
Ovarian Cancer Research Alliance
Strathmore Health Strategy
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[1] Offit K, et al. Regulation of Laboratory-Developed Tests in Preventive Oncology: Emerging Needs and Opportunities. *J Clin Oncol*. 2023;41(1):11-21.
[2] Genzen JR, Mohlman JS, Lynch JL, et al. Laboratory-Developed Tests: A Legislative and Regulatory Review. *Clin Chem*. 2017;63(10):1575-1584.
[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. Accessed August 23, 2023.
[4] Congressional Research Service. *FDA Regulation of Laboratory-Developed Tests (LDTs)*. 2022. https://crsreports.congress.gov/product/pdf/IF/IF11389. Accessed August 28, 2023.
[5] Association of American Medical Colleges. *Congress Avoids Shutdown, Approves Continuing Resolution Through Mid-December*. 2022. https://www.aamc.org/advocacy-policy/washington-highlights/congress-avoids-shutdown-approves-continuing-resolution-through-mid-december. Accessed August 24, 2023.
[6] 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 August 24, 2023.
[7] 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 August 28, 2023.
[8] Medical Device Amendments of 1976. P.L. 94-295.
[9] 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 August 23, 2023.

[10] The PEW Charitable Trusts. *The Role of Lab-Developed Tests in the In Vitro Diagnostics Market.* October 22, 2021. https://www.pewtrusts.org/en/research-and-analysis/reports/2021/10/the-role-of-lab-developed-tests-in-the-in-vitro-diagnostics-market. Accessed August 23, 2023.

[11] 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. Accessed August 23, 2023.

[12] Shuren J, Stenzel T. Covid-19 Molecular Diagnostic Testing – Lessons Learned. *N Engl J Med*. 2020;383(17):e97(1)-e97(3).

[13] 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-non-invasive-prenatal-screening-tests-may-have-false-results-fda-safety-communication. Accessed August 30, 2023.

[14] 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 August 28, 2023.

[15] 42 C.F.R U.S.C. § 493.1253. Standard: Establishment and Verification of Performance Specifications.

[16] 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 September 11, 2023.

[17] CLIA. Number of CLIA Certificate of Accreditation Laboratories by Accreditation Organization. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/statacrd.pdf. Accessed September 13, 2023.

[18] College of American Pathologists. Laboratory Accreditation Program. https://www.cap.org/laboratory-improvement/accreditation/laboratory-accreditation-program. Accessed September 11, 2023.

[19] The Joint Commission. Laboratory Accreditation. https://www.jointcommission.org/resources/news-and-multimedia/fact-sheets/facts-about-laboratory-accreditation/. Accessed September 11, 2023.

[20] 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 August 23, 2023.

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