



May 30, 2023

Robert M. Califf M.D., MACC  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
*Submitted via email to:* [commissioner@fda.hhs.gov](mailto:commissioner@fda.hhs.gov)

Re: Stakeholder Groups Urge the FDA to Pass Regulation on Laboratory-Developed Tests

Dear Dr. Califf,

We write on behalf of a broad group of public interest organizations to urge the Food and Drug Administration (FDA) to develop regulations for laboratory-developed tests (LDTs) in the event that legislation to regulate such tests does not progress in Congress.

As you know, LDTs are diagnostic tests that are developed and performed in a single laboratory.<sup>1</sup> These tests have become increasingly important in clinical practice, but they put patients at risk and drive up healthcare costs when they perform poorly or are not supported by science.<sup>2</sup>

To ensure that LDTs are safe and effective before they are marketed, the FDA has the authority to regulate them under the Federal Food, Drug, and Cosmetic Act (FD&C Act).<sup>3</sup> Historically, however, the agency has chosen not to use its authority to regulate most LDTs because early tests were fairly simple and used on a small number of patients.<sup>4</sup> However, the availability and complexity of these tests have grown over time and many have been found to be inaccurate.

In 2015, the FDA published a report presenting 20 case studies of LDTs that caused or may have caused harm to patients.<sup>5</sup> In some cases, patients were told they had conditions such as Lyme disease and ovarian cancer that they did not have (false-positives); in others, the tests missed patients' life-threatening conditions like breast cancer (false-negatives). In other tests, the biomarkers measured had no proven relevance to the diseases that tests claimed to detect, or their associated treatments. Since the report was published, many more LDTs have been developed and used without oversight on an increasing number of patients.<sup>4</sup> Some of these tests include COVID-19 diagnostic tests<sup>6</sup> and genetic non-invasive prenatal screening tests,<sup>7</sup> many of which have produced inaccurate results.

Labs performing clinical tests are regulated by the Centers for Medicare and Medicaid

Services (CMS), but that agency regulates labs themselves rather than the accuracy or reliability of tests. The CMS requires labs to establish the performance of the test under laboratory conditions, but it does not assure that the test performs well clinically.<sup>8</sup> For example, if a blood test measuring proteins shed by pancreatic cancer cells is used to diagnose pancreatic cancer, the CMS would only require that the lab establish how well the test detects the proteins, not whether the detection of the proteins is a reliable way to diagnose pancreatic cancer. If LDTs were reviewed as medical devices, performance characteristics and clinical validity would be overseen by the FDA. Under the FD&C Act, the FDA could also oversee manufacturer claims, labeling, and adverse event reporting.

The FDA has proposed regulation for these tests in the past. In 2014, it released a draft guidance that outlined a risk-based approach to premarket review of LDTs and a process for labs to notify the FDA of such tests.<sup>3</sup> Unfortunately, pressure from industry and Congress stopped the FDA from finalizing this guidance.<sup>9</sup> As explained in a subsequent discussion paper at the end of the Obama administration, the FDA chose not to finalize its guidance in order to permit additional public discussion of an appropriate approach and to give Congress the chance to provide a legislative solution.<sup>10</sup>

Yet Congress has failed to provide such a solution. Since the release of the FDA's discussion paper, there has been significant public debate over LDT regulation, and the introduction of two bills that ultimately did not pass.<sup>11,12</sup> Last year, the Verifying Accurate Leading-edge IVCT Development Act of 2021 (VALID Act) was approved by the Senate Committee on Health, Education, Labor, and Pensions as part of the Medical Device User Fee Amendments (codified as the FDA Safety and Landmark Advancements Act of 2022 (FDASLA Act)).<sup>13</sup> It established a risk-based modern framework for all diagnostic tests, including LDTs. Under this tiered system, high-risk tests undergo individual premarket review, most moderate-risk tests can be introduced once the developer is granted a one-time technology certification based on review of the developer's overarching procedures and a single representative assay, and low-risk tests are exempt from review. The bill also mandated adverse event reporting by developers and transparency through public test listings with performance summaries. It was ultimately not included in the FDASLA Act<sup>14</sup> or in the Omnibus Budget Reconciliation Act that followed.<sup>15</sup>

The most recent version of the VALID Act, which is generally consistent with previous versions, was introduced in the House in March 2023.<sup>16</sup> Ideally, passage of this legislation would provide the FDA with a clear statutory authority to regulate LDTs. However, past experience suggests that such legislation may not pass, especially in the current political climate and given the technical complexity of the issues involved. In the absence of Congressional action, it is imperative that the FDA revisit its stance, and take steps to ensure that LDTs are accurate and reliable.

We applaud the FDA's past efforts to regulate LDTs and, if a strong bill does not progress in Congress, urge the agency to implement regulation for LDTs that includes requirements for analytical and clinical validation, quality control, adverse event reporting, and transparency. Such regulation would help close the gap created by the lack of adequate independent oversight and ensure that accurate LDTs are marketed to consumers and used to guide patient care, while also promoting innovation and competition in the diagnostic

testing industry.

Sincerely,

Center for Science in the Public Interest  
AllergyStrong  
Center for Food Safety  
CURED NFP (Campaign Urging Research for Eosinophilic Diseases)  
Elijah-Alavi Foundation  
FARE (Food Allergy Research and Education)  
Food Allergy & Anaphylaxis Connection Team  
Food Equality Initiative  
International FPIES Association (IFPIES)  
National Center for Health Research  
Patient Safety Action Network  
Strathmore Health Strategy  
The TMJ Association  
USA Patient Network  
U.S. PIRG  
Washington Advocates for Patient Safety

CC:

Jeffrey Shuren, Director of FDA's Center for Devices and Radiological Health (CDRH)  
Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, CDRH

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<sup>1</sup> U.S. Food and Drug Administration. *Laboratory Developed Tests*. 2018. <https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests>. Accessed April 3, 2023.

<sup>2</sup> Offit K, et al. Regulation of Laboratory-Developed Tests in Preventive Oncology: Emerging Needs and Opportunities. *J Clin Oncol*. 2023;41(1):11-21.

<sup>3</sup> 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 April 3, 2023.

<sup>4</sup> 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 April 3, 2023.

<sup>5</sup> 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](https://www.nila-usa.org/images/nila/The%20Public%20Health%20Case%20for%20FDA%20Oversight%20of%20LDTs%20110915(2)_508ed%20(1).pdf). Accessed April 3, 2023.

<sup>6</sup> Adashi EY, Cohen IG. SARS-CoV-2 Laboratory-Developed Tests: Integrity Restored. *JAMA*. 2022;327(13):1229-1230.

<sup>7</sup> 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 April 4, 2023.

<sup>8</sup> 42 C.F.R § 493.1253. Standard: Establishment and Verification of Performance Specifications.

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<sup>9</sup> Genzen JR, Mohlman JS, Lynch JL, et al. Laboratory-Developed Tests: A Legislative and Regulatory Review. *Clin Chem*. 2017;63(10):1575-1584.

<sup>10</sup> U.S. Food and Drug Administration. *Discussion Paper on Laboratory Developed Tests (LDTs)*. 2017. <https://www.fda.gov/media/102367/download>. Accessed April 4, 2023.

<sup>11</sup> S.3404/H.R.6102. VALID Act of 2020.

<sup>12</sup> S.2209/H.R.4128. VALID Act of 2021.

<sup>13</sup> S.4348. FDASLA Act of 2022.

<sup>14</sup> 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 April 4, 2023.

<sup>15</sup> 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 April 4, 2023.

<sup>16</sup> H.R.2369. VALID Act of 2023.