



December 1, 2023

Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

RE: Medical Devices; Laboratory Developed Tests, Docket No. FDA-2023-N-2177

Dear Commissioner Califf,

On behalf of the LUNGeVity Foundation, the nation’s preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the more than 230,000 Americans diagnosed with lung cancer each yearⁱ and over 600,000 Americans living with the disease,ⁱⁱ we appreciate the opportunity to submit comments in response to the proposed rule: Medical Devices; Laboratory Developed Tests, Docket No. FDA-2023-N-2177. LUNGeVity submits these comments specifically from the perspective of patients with lung cancer, for whom the accuracy and reliability of diagnostic tests used to direct their treatment is of paramount importance.

Treatment of lung cancer is at the leading edge of precision medicine, with several biomarker-driven treatment options. Approximately fifty percent of patients with non-small cell lung cancer (NSCLC, the most common type of lung cancer) harbor a biomarker with a corresponding FDA-approved targeted therapy.ⁱⁱⁱ Targeted therapies are typically linked to FDA-approved companion diagnostics: tests used to identify patients most likely to benefit from that particular treatment. However, the one-drug-one-test paradigm is not reflective of real-world clinical practice, where in-house, multi-analyte laboratory-developed tests (LDTs) are frequently used to direct treatment decisions.

Since the regulatory framework for medical devices was established under the Medical Device Amendments of 1976, the FDA has exercised enforcement discretion regarding LDTs. Over the past decade the Agency has made several moves to bring LDTs under its oversight, recognizing that the number, complexity, and breadth of use of LDTs has increased dramatically since it began its policy of enforcement discretion. In addition to issuing guidance documents and a discussion paper, FDA most recently worked with Congress and engaged with stakeholders, including patient advocates, to develop legislation which created a framework specifically for LDT (or in vitro clinical test (IVCT)) regulation. Despite enjoying support from many in the diagnostics community, this legislative approach to ensuring FDA oversight of LDTs stalled and the Agency has now moved forward with notice-and-comment rulemaking to end enforcement discretion for LDTs.

While LUNGeVity understands FDA’s rationale for pursuing this course of action, **we support an approach to LDT oversight that balances the dual priorities of patient safety and continued innovation in test development and question whether the current medical device regulatory framework is suited for that purpose.** Herein we lay out concerns that should be addressed in the final rule and/or through subsequent guidance.



Regulation of LDTs should not hinder patient access to accurate, reliable biomarker tests

In lung cancer, where biomarker testing is necessary for determining the most appropriate treatment option, LDTs are frequently used for biomarker detection even when FDA-approved tests exist.^{iv,v} The Agency should carefully consider whether the proposed timeframe for phasing out enforcement discretion is adequate for clinical laboratories to prepare application packages for all of the tests they offer, and if submission for **all** tests is necessary. Clinical labs may not have sufficient staff or regulatory expertise to fulfill the proposed new regulatory requirements. If the fees, resource demands, and timelines are prohibitive, labs may cease offering high-quality lung cancer biomarker tests because of onerous requirements, to the ultimate detriment of patients.

In addition to the economic and administrative burdens the proposed rule may place on test developers, we are concerned about the FDA's capacity to review the number of applications it expects to receive in a timely manner. It may be necessary to increase the duration of the phase-out period for enforcement discretion for premarket review, and/or to consider grandfathering of certain LDTs, to ease the burden on both the Agency and labs and ensure the rule does not disrupt patients' access to accurate biomarker testing. **We suggest that the FDA allow grandfathering for existing LDTs that have demonstrated concordance with FDA-approved companion diagnostics** (see, for example, Torlakovic et al.^{vi})

Regulation of LDTs should incorporate flexibilities for test modifications

As diagnostic tests often require modification to improve performance and address changing clinical needs, **we encourage the FDA to provide opportunities for developers to make certain modifications to diagnostic tests without unnecessary regulatory hurdles.** The FDA has previously expressed openness to the submission of prospective change protocols, wherein test developers outline anticipated modifications and the procedures they would use to implement them.^{vii,viii} If approved, modifications made in accordance with the change protocol would not require a new submission, with only changes significantly altering the intended use or performance specifications requiring review. Change protocols or similar mechanisms allowing flexibilities for modifications should be included and detailed by the Agency in future guidance.

LUNGevity supports a legislative approach to LDT regulation reform

We believe that a legislative solution to diagnostics reform could strike a better balance between promoting patient safety and ensuring regulatory flexibilities for both test developers and the FDA than the proposed rule does. Furthermore, legislation can clarify and codify that FDA has both the authorities and resources necessary to effectively oversee the development and marketing of diagnostic tests.

For example, LUNGevity supported the Verifying Accurate, Leading-edge IVCT Development (VALID) Act of 2022, which established a new category of products (i.e., IVCTs) encompassing all *in vitro* diagnostics, including LDTs, along with a new, fit-for-purpose regulatory framework. Additionally, VALID outlined flexible pathways for marketing diagnostic tests, such as technology certification, to accelerate the delivery of innovative diagnostics to patients without unnecessary regulatory hurdles. Incorporating these kinds of innovations—which would improve the ability of test developers to keep pace with scientific advancements—into current regulations is only possible through legislation as it would require Congressional approval.



In addition to supporting the bill itself, we appreciated the extensive engagement among various stakeholders involved in shaping VALID. **LUNGEvity encourages FDA to continue engaging with all stakeholders in the diagnostics community to pursue a legislative option for regulation of LDTs in parallel with rulemaking.**

We appreciate the opportunity to provide these comments in response to the Agency’s proposed rule. Please feel free to reach me at ae Ferris@lungevity.org or at 240-454-3103 with any questions.

Sincerely,

Andrea Stern Ferris
President and Chief Executive Officer
LUNGEvity Foundation

ⁱ Howlander N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.

ⁱⁱ Centers for Disease Control and Prevention. United States Cancer Statistics. Available at <https://gis.cdc.gov/Cancer/USCS/#/Prevalence/>.

ⁱⁱⁱ Thai AA, Solomon BJ, Sequist LV, et al. Lung cancer. *Lancet* 2021; 398(10299):535-554.

^{iv} Audibert C, Shea M, Glass D, et al. Use of FDA-approved vs. lab-developed tests in advanced non-small cell lung cancer. *Journal of Clinical Oncology* 2016; 34(15) suppl.

^v Mino-Kenudson M, Stang NL, Daigneault JB et al. The International Association for the Study of Lung Cancer Global Survey on Programmed Death-Ligand 1 Testing for NSCLC. *Journal of Thoracic Oncology* 2021; 16(4):686-696.

^{vi} Torlakovic E, Lim HJ, Adam J, et al. “Interchangeability” of PD-L1 immunohistochemistry assays: a meta-analysis of diagnostic accuracy. *Modern Pathology* 2020; 33(1):4-17.

^{vii} U.S. Food and Drug Administration. Discussion Paper on Laboratory Developed Tests (LDTs). 2017 Jan 13. Available at <https://www.fda.gov/media/102367/download>.

^{viii} U.S. Food and Drug Administration. Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions: Draft Guidance for Industry and Food and Drug Administration Staff. 2023 Apr. Available at <https://www.fda.gov/media/166704/download>.