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**Via Electronic Submission**

December 4, 2023

Robert Califf, MD  
Commissioner  
U.S. Food and Drug Administration  
5630 Fishers Lane Room 1061  
Rockville, MD 20852

**Subject: Medical Devices; Laboratory Developed Tests (Docket No. FDA-2023-N-2177)**

Dear Dr. Califf,

The Association for Clinical Oncology (ASCO) appreciates the opportunity to respond to the Food and Drug Administration's (FDA) proposed rule to amend current regulations by phasing out the Agency's general enforcement discretion approach for laboratory developed tests (LDTs). ASCO has advocated for many years for FDA regulatory oversight of LDTs. The existing role of the Clinical Laboratory Improvement Amendments (CLIA) is *necessary and should be complementary* to FDA's regulatory oversight of all in vitro diagnostics (IVDs), including LDTs. The FDA's oversight, however, is also *necessary* to ensure the safety and effectiveness of LDTs used for directing critical treatment decisions. While the CLIA program continues to ensure good laboratory practices and quality laboratory testing of human samples; clinicians, patients, and their caregivers rely on the FDA's public health mission to ensure that therapeutics and devices are safe and effective. The FDA and CLIA roles for LDTs differ: the FDA ensures appropriate clinical validation of LDTs, while the Centers for Medicare and Medicaid Services (CMS) ensures that laboratories continue to meet minimum performance standards.

ASCO is a national organization representing nearly 50,000 oncology professionals who care for patients with cancer. Our members are committed to ensuring equitable access to high quality evidence-based care for the prevention, diagnosis, and treatment of cancer for all Americans through research and education. As a provider organization we represent our members who care for millions of patients across the country, who rely on accurate and

reliable IVDs, including LDTs, over the course of their medical treatments. We agree with the patient concerns FDA raised in the rationale for the proposed rule, and that the U.S. public health would benefit from a regulatory framework for LDTs to ensure patient safety. Our support for the FDA’s proposed rule aligns with our history of developing evidence-based clinical practice guidelines. ASCO was one of the first organizations to establish clinical practice guidelines for the use of tumor biomarkers.<sup>1</sup>

As cancer care becomes more complex and increasingly personalized, it is *more important than ever* to ensure that new diagnostic tests are of the highest quality. According to November 20, 2023, data from the National Cancer Institute, the FDA has approved over 180 agents that require assessment of a tumor biomarker for use against more than 300 types of cancer.<sup>2</sup> Many of these drugs/biologics and indications were approved based on pivotal clinical trials that used FDA-cleared companion diagnostic (CDx) tests to select patients. The FDA clears a CDx because it determines that the test is “essential for the safe and effective use of a corresponding therapeutic product.”<sup>3</sup> For many such targeted agents, academic and commercial laboratories rapidly develop LDTs for the relevant tumor biomarkers. Redundant LDTs in drug development also complicate oversight and should be avoided where possible. Furthermore, LDTs lack the same level of validation as the CDx for many reasons (including, but not limited to, absence of information on the CDx’s minimum performance standards, the legal void caused by FDA regulatory discretion, and CMS regulation under CLIA). As a result, patients, their caregivers, and their clinicians may lack vital, validated predictive and prognostic evidence when using LDTs to accurately identify patients who may be likely to benefit from the targeted treatment. In some cases, the presence or absence of a validated test has put at risk patients’ survival and quality of life (i.e., all aspects of how people feel and function, including many aspects that are not reliably measured, such as financial and time toxicities).

Without regulatory reform, the currently outdated oversight of the development and quality of these tests will continue to risk proliferation of inaccurate and unreliable tests, placing patients’ survival and quality of life at risk. To that end, we support FDA’s efforts to modernize regulatory oversight of LDTs, more specifically high-risk LDTs. We provide our responses below to the questions posed by the Agency.

**What would be the public health rationale for generally exercising enforcement discretion with respect to premarket review for LDTs (i.e., “grandfathering”); and for maintaining the general**

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<sup>1</sup> American Society of Clinical Oncology Tumor Markers Expert Panel: Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. J Clin Oncol 14: : 2843,1996 -2877, (adopted on May 17, 1996 by the American Society of Clinical Oncology)

<sup>2</sup> National Cancer Institute. *List of Targeted Therapy Drugs Approved for Specific Types of Cancer*. November 20, 2023. Available at <https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/approved-drug-list>. Last accessed November 28, 2023.

<sup>3</sup> U.S. Food and Drug Administration. *Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products: Guidance for Industry*. April 2020. Available at <https://www.fda.gov/media/120340/download>

**enforcement discretion approach with respect to premarket review and QS requirements for a subset of LDTs (e.g., low and moderate risk LDTs)?**

ASCO emphatically supports the need for FDA premarket regulatory review for IVDs, particularly high-risk LDTs. ASCO is concerned that many LDTs may fail to achieve the validation standards and institutional safeguards that originally justified FDA’s general enforcement discretion approach. As a result, we support FDA’s proposal to assert its regulatory authority for these high-risk tests due to its mission as a public health agency.

The National Academy of Sciences, as part of its scientific charge, was concerned enough about the threat to the public’s and individual patients’ health that it issued a report in 2016, *Biomarker Tests for Molecularly Targeted Therapies*. This report called for appropriate regulatory oversight to ensure that the tests are accurate, reliable, properly validated, and appropriately implemented in clinical practice.<sup>4</sup> Because there have been failed attempts, both legislative and regulatory, to establish an appropriate, modern regulatory framework for LDTs, there remain concerns that tests developed prior to implementation and enforcement of a final rule would leave high-risk tests on the market without adequate oversight. Over this time ASCO has consistently advocated for a flexible, risk-based regulatory framework that would also incentivize and improve the development of innovative, advanced, reliable tests.

We believe a three-risk classification model is appropriate. High-risk tests are increasingly being used to guide therapeutic decisions for people with cancer. As a result, people at risk for, or diagnosed with, cancer could be caused serious or irreversible harm, prolonged disability, or death based on an inaccurate test result. High-risk tests must be regulated to ensure they are thoroughly validated and of the highest quality. Furthermore, the public, including people at risk for or living with cancer, their caregivers, and clinicians, should have access to the evidence used to validate the tests; and laboratory professionals should understand the minimum performance characteristics of these tests. Finally, we believe the premarket requirements should be consistent with the risk-category of the test.

**Is there a public health rationale to have a longer phaseout period for IVDs offered as LDTs by small laboratories (i.e., laboratories with annual receipts below a certain threshold e.g. \$150,000)?**

While we appreciate that implementing regulatory change requires resources, we are currently unaware of data or information that warrants extending the timeline or the phases proposed in the rule. The proposed phasing out of FDA’s current enforcement discretion over 4 years is appropriate and should be sufficient to allow time for guidance and compliance. No matter the size of the laboratory, high-risk IVDs

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<sup>4</sup> National Academies of Sciences, Engineering, and Medicine. 2016. *Biomarker Tests for Molecularly Targeted Therapies: Key to Unlocking Precision Medicine*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/21860>.

and LDTs are classified as such because they have potential to jeopardize public health and safety. Risk of public health and safety should not be based on laboratory size. In the area of therapeutics, the FDA exercises premarket regulatory authority for all companies. We believe the FDA should be allowed the same discretion to regulate high-risk tests based on FDA's determination of the risk to the public health. The general public's health and the health of people at risk for or living with diseases/conditions should continue to be the cornerstone for FDA's regulatory enforcement.

**How to appropriately define and characterize an Academic Medical Center (AMC) laboratory, whether there are any considerations to support continuing enforcement discretion for AMC laboratories, and any data or information supporting a public health rationale for such an approach?**

All definitions employed by the FDA in this proposed and the final rule should be based on the risk level of the test in question, not on how a laboratory is or is not organized. Regulation of healthcare services, organizations, and providers occurs at multiple levels of US and state government. Regulating based on terms such as "small" and "academic medical center" as the basis for asserting regulatory authority would put the FDA in an endless tailspin of legal challenges and necessitating tracking of legal, regulatory, and organizational changes.

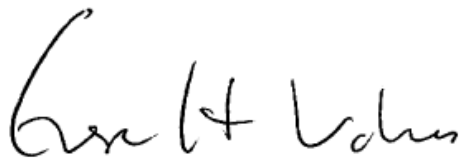
Furthermore, LDTs are no longer designed and solely utilized in a single laboratory. This partial enforcement discretion and consideration will almost certainly further exacerbate health inequities. Increased oversight, on the other hand, could ensure *adequate representation* of the intended use population in validation and utility studies – thereby improving external validity and enhancing protections for populations who have been historically marginalized or experienced inequities.

**How might FDA leverage programs such as the New York State Department of Health Clinical Laboratory Evaluation Program or those within the Veterans Health Administration to allow continuation of the enforcement discretion approach for certain tests?**

We believe the regulatory framework for all IVDs, including LDTs, should be a **single, flexible, risk-based regulatory framework**. Using this approach will help ensure that all diagnostic tests are reviewed according to the same standards established for each risk category. In addition, incorporation of the stakeholders who will be involved from the intended-use population and transparency of the process and conclusions (as the FDA does with its public advisory meetings) will help ensure public trust. Furthermore, entities involved in administering the process should meet a high standard of protections against conflicts of interest. If the FDA utilizes third party review programs, we believe the regulatory standards should be set by the FDA to ensure consistency and public oversight.

We thank you again for the opportunity to contribute to the FDA's proposal to regulate LDTs as medical devices to address the imbalance in oversight of IVDs and to protect public health. Please contact Shimere Williams Sherwood at [Shimere.Sherwood@asco.org](mailto:Shimere.Sherwood@asco.org) with any questions and for further discussions.

Sincerely,

A handwritten signature in black ink that reads "Everett E. Vokes". The signature is written in a cursive style with a large initial "E".

Everett E. Vokes, MD, FASCO

Chair of the Board, ASCO Association for Clinical Oncology