December 4, 2023

Robert M. Califf, MD
Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Dear Dr. Califf:

Re: Docket No. FDA–2023–N–2177 for ‘‘Medical Devices; Laboratory Developed Tests.’’
Submitted via regulations.gov

On behalf of the National Independent Laboratory Association (NILA) and the American Association of Bioanalysts (AAB), thank you for the opportunity to submit comments in response to the Food and Drug Administration's (FDA) proposed rule *Medical Devices; Laboratory Developed Tests, RIN 0910-AI85*. The rule proposes to phase out the FDA's long standing general enforcement discretion of laboratory developed tests (LDTs) such that LDTs would be subject to the same regulation as in vitro diagnostic products (IVDs).

NILA and AAB strongly object to FDA's approach to the regulation of LDTs as outlined in the proposed rule and cannot support it in its current form. The proposed regulation asserts that LDTs are medical devices and should therefore be regulated under the same framework as all other medical devices. LDTs are not medical devices and should not be regulated as such.

NILA represents regional, community, and specialty clinical laboratories across the United States that perform laboratory testing for physicians, hospitals, skilled nursing facilities, and other health care professionals. NILA members serve a wide variety of communities and patient populations, and many of those communities are not served by large national laboratories. Community, regional, and specialty clinical laboratories play a vital role in providing testing services to patients in rural areas, underserved urban areas, mid-and small-sized cities, congregate facilities, and critical access hospitals. Founded in 1956, AAB members are clinical laboratory directors, managers, supervisors, technologists, and technicians. AAB, like NILA, is dedicated to serving community, regional, and specialty clinical laboratories.

The comments below outline NILA and AAB's position that LDTs are not medical devices and laboratories are not commercial manufacturers and describe the consequences that implementation of this proposed rule would have on patients, providers, and laboratories. The proposed regulations will place undue administrative and financial burden on laboratories at a cost that will stifle innovation and will jeopardize certain aspects of patient care. The proposed regulatory requirements will cause many laboratories to drop tests from their test menus, leaving a gap in patient access to testing at a time when patient access to clinical laboratory testing is essential.

LDTs identify new and dangerous substances during the current opioid crisis, identify emerging infectious diseases, and provide myriad other clinically important information needed in the interest of public health. For many LDTs, there is no comparable IVD test kit—and contrary to the assertion made by the FDA in the narrative of the proposed rule, the changes proposed will not spur innovation from traditional medical device manufacturers to fill those gaps. **We strongly urge the FDA to withdraw the proposed regulation, and instead collaborate with stakeholders and policymakers to develop a solution that works for everyone, including a solution that acknowledges the unique nature of LDTs and prioritizes patient care.**

LDTs are not Manufactured IVD Test Kits

LDTs are defined as in vitro diagnostic tests that are designed, produced, and used within a single laboratory. Unlike commercial IVD products, LDTs are developed and used by professional laboratory personnel who provide expert analyses and are not produced or marketed for use outside of the originating laboratory. The lack of marketing and sales to other laboratories further differentiates LDTs from IVDs—a distinction that is crucial to understanding why LDTs do not fit into the category of medical devices. The primary role of LDTs is to detect and/or quantify substances within the human body, aiding in disease detection, health condition assessment, monitoring of drug treatments and other testing processes. In fact, over 83 percent of LDTs offered by NILA and AAB-member laboratories serve these purposes. The development and usage of LDTs are heavily reliant on the expertise of professional laboratory personnel. These professionals are not only involved in the design and development of LDTs but also play a critical role in their continuous improvement and performance.

LDTs play an irreplaceable role in patient care as manufactured and marketed IVD test kits do not cover the full spectrum of patient clinical needs and given the limited utility of IVD tests, may quickly become outdated, particularly when used for drug testing. Because LDTs are tailored to specific clinical needs and are developed based on direct laboratory experience and expertise, LDTs are often more accurate, reliable, and relevant to patient care than FDA-approved IVDs. Following the ordering and subsequent review of results of an LDT, physicians use their clinical judgment to interpret the test results in the context of the patient's overall health status. For example, LDTs not IVD test kits, are used to detect the rash of synthetic fentanyl and other drugs fueling the ongoing opioid epidemic. Many of these substances are not detectable with FDA-cleared test kits. In fact, technologically, most LDTs are not amenable to IVD manufactured tests. Further, such testing is performed by a limited number of laboratories nationwide, limiting the interest from IVD manufacturers to produce test kits for newly emerging drugs of abuse. For a handful of drug screening tests, there are only one or two laboratories in the country that perform them. The laboratories performing drug testing rely on LDTs because no manufacturer is going to design, develop, and approve a test to market it to one laboratory—the market simply will not support it. Yet, patients and providers rely on these life-saving tests. Without LDTs, public health officials and physicians would not have access to tests that can identify new and dangerous substances and provide other clinically important information, thus leaving the public at risk and slowing opportunities that would have a critical impact on public health.

Considering these factors, it becomes evident that LDTs, owing to their unique characteristics and the context in which they are developed and used, should not be categorized as medical devices. LDTs are distinct in their design, purpose, and application, and are intricately linked to the expertise of laboratory professionals and the clinical judgment of health care providers. Classifying LDTs as medical devices not only misrepresents their nature but also leads to regulatory challenges that do not align with the actual use and purpose of LDTs in clinical settings.

Section Summary Highlights

- **LDTs and IVD manufactured tests are not the same and should not be subject to the same regulatory pathway. LDTs are not meant to be used as standalone, automated tests with little to no expertise provided for their use. This is in direct contrast to IVD manufactured tests.**
- **IVD manufacturers lack financial incentives to develop and sell tests where the commercial market to use them is too small.**
- **LDTs play a critical role in public health and safety. Clinicians rely on such tests as part of a holistic approach to patient care.**
- **LDTs are one part of a clinician's overall assessment of a patient.**

Independent Laboratories are not Commercial Manufacturers

Given the types of laboratories (community, regional, and specialty and mostly independently owned and operated) that NILA and AAB represent, we can confirm that almost all NILA and AAB laboratories do not have the resources—human or financial—to undertake the FDA's medical device premarket approval process. After three years of a global pandemic, many NILA and AAB member laboratories continue to be short-staffed. If laboratories are forced to undertake a time consuming new regulatory pathway, many will be forced to decide if adhering to the regulation is worth the cost. NILA and AAB members have stated they would stop offering LDTs altogether because they cannot afford to hire the staff necessary to put their LDT menu through the medical device regulatory pathway and process. For those laboratories that attempt the process, the few staff that the laboratories have would be forced to spend valuable time and resources filing paperwork and responding to FDA inquiries regarding 510(k) clearance and PMA approvals rather than performing the actual functions of the laboratory—all of which will delay patient testing and care.

The implementation of this rule may have negative effects on community, regional, and specialty clinical laboratories, and ultimately result in job losses in critical communities throughout the United States. The operating margins of NILA and AAB member laboratories are often quite thin. The revised oversight of LDTs, if imposed, would create an administrative and financial burden that many laboratories, particularly those that are specialized and independent, would not be able to withstand. While NILA and AAB member laboratories have lower revenue than the large national laboratories, some of their testing menus can range into the thousands. For example, NILA has a member laboratory that currently lists over four hundred LDTs on its test menu encompassing approximately 2,500 tests when different matrices are accounted for, all of which are toxicology tests. The paperwork nightmare to apply for FDA approval for all 2,500 of those tests is best described as insurmountable. Staff time alone would cost hundreds of thousands of dollars, without accounting for FDA user fees. Many such laboratories would not be able to support the staff required to adhere to the regulations.

Section Summary Highlights:

- **Community, regional, and specialty laboratories performing LDTs will face financial challenges under the proposed FDA regulations, leading to reduced test offerings, overwhelming costs, or closures with nationwide job losses.**
- **Patient care will suffer when laboratories cut their testing menus.**

Innovation will Suffer

The FDA's proposed rule claims that it will increase innovation, but this is simply not true. Imposing additional regulations on LDTs risks making development prohibitively expensive, especially for community, regional, and specialty clinical laboratories. The cost for the development of an average LDT may range from $10,000 to $60,000. Overlay of additional significant FDA user fees would put the development of new and innovative LDTs out of reach for many laboratories. Recovery of research and development costs is part of the calculus for a laboratory to decide whether to move forward with test development. Many LDT laboratories never recover the cost of developing a particular test, but new tests may complement other tests that offset such losses. Failure to recognize such factors will hinder patient access to innovative diagnostic and treatment technologies, particularly in the fields of cancer and orphan diseases. For many diseases and conditions, an LDT is the only option for testing. For example, laboratories have developed LDTs to detect more than four hundred different allergens, most of which are not available from IVD manufacturers. These unique tests help physicians formulate better treatments for patients. Laboratories have improved the quality of allergy detection with LDT technologies that manufacturers have been reluctant to adopt due in part to the regulatory burden of FDA review.

The FDA premarket approval process is time consuming and costly. Device manufacturers are businesses that must weigh the costs associated with FDA approval of IVD test kits with the return on investment they can recoup by selling kits to clinical laboratories. LDTs are not high volume, making a costly regulatory process for approval untenable for laboratories. If a test is not performed in high enough volume, it is unlikely a manufacturer is going to take on the costs of approval for such a small market. If large scale medical device manufacturers choose not to shoulder these costs, community and regional laboratories should not be forced to undertake this process. For such laboratories, developing and performing tests carries a moral obligation to patients. Unfortunately, if the proposed FDA LDT regulations are implemented, laboratories will need to make difficult decisions that pit financial cost against the cost of not having critical laboratory tests for patient care. Laboratories will be forced to stop developing essential clinical laboratory tests.

Section Summary Highlights:

- **Although many LDTs aid in clinical decision-making, imposing additional FDA-related costs could hinder rather than promote the development of new test processes.**
- **With FDA oversight, LDT laboratories will be confronted with moral ramifications of test removal.**

LTDs are Reliable and Already Regulated

The proposed rule is duplicative and unnecessary given the existing robust regulatory framework already in place. Laboratories conducting complex clinical testing are already under the stringent regulatory requirements of the federal Clinical Laboratory Improvement Amendments (CLIA). State-level regulations and professional society guidelines further ensure that laboratories maintain high standards. This multi-layered regulatory environment guarantees that patients receive accurate and reliable laboratory testing services.

Many LDTs fall within the purview of existing CLIA and state-specific guidelines, effectively overseeing the analytical validity of each test. One such example of this is CLIA'S proficiency testing requirements. CLIA mandates this process for laboratories, which is a critical external quality control measure. This

process involves analyzing unknown samples and having the results graded by an HHS-approved proficiency testing program. This ensures the validity and accuracy of LDTs in real-world scenarios. In cases where external proficiency tests are unavailable, laboratories are required to develop alternative methods to validate their tests. Additionally, all CLIA-based laboratories are required to have quality management systems (QMS) that ensure effective quality assurance, including corrective action programs, when tests fall out of validated limits. All these factors ensure the validity and accuracy of LDTs in real-world scenarios. Prior to releasing any LDT result, laboratories are required to establish the test's analytical validity within their specific environment. This validity is also reviewed biennially by CMS or an agency acting on CMS' behalf, ensuring continuous quality assurance and improvement. A detailed examination of the CLIA testing process, along with state processes (such as those conducted by The New York State Department of Health), illustrates the thoroughness of existing regulations. Additionally, CLIA assessment administered through CLIA-approved accrediting agencies, such as the College of American Pathologists (CAP), COLA, and the Joint Commission, must account for clinical validity. In addition, laboratories whose tests are approved by the New York State Department of Health have the requirement to address both clinical utility and validity. These existing frameworks render additional FDA oversight redundant.

In its preamble, the FDA cites specific examples of the use of LDTs that have led to poor patient outcomes. While it is true that such examples exist, these examples are not typical. Most importantly, such examples do not reflect the majority of LDTs currently available to clinicians and other users and drastically changing an entire regulatory pathway to address a few underperforming tests is not good policy. In fact, there is ample evidence demonstrating that the FDA's "approval" does not guarantee successful testing or products. In fact, the FDA approved an LDT for Theranos, including a device, analytical software, and proprietary test tubes. The company outcome is well-documented. Further, review of CAP proficiency testing summary reports (PSRs) demonstrates FDA-cleared kits for the same analyte can provide widely divergent results.

Section Summary Highlights:

- **Current LDT regulations encompass areas the FDA proposes to regulate to avert significant patient impact.**
- **Proficiency testing and quality management systems monitor and assess test accuracy and ongoing improvements, including corrective actions for non-conforming tests.**
- **Using examples of poorly performing LDTs to justify FDA regulation is misleading and not representative of the entire industry.**
- **Laboratories that take extraordinary steps to assure quality improvements have already voluntarily taken steps to assure LDTs that are safe and effective,**

Recommendations

As outlined above, NILA and AAB do not support the rule in its current form. While our stated preference is for the rule to be rescinded to facilitate a dialogue between stakeholders and policymakers on a sustainable path forward, we understand the importance of commenting on ways to improve the rule from its current form. Therefore, NILA and AAB offer the following suggested recommendations:

1. **Develop a true risk-based framework:** As outlined above, LDTs are not medical devices and should not be forced through a regulatory system that equates them as such. Any imposed regulation of LDTs requires a separate risk-based framework that clearly distinguishes LDTs based on the risk to the patient. NILA and AAB support a risk-based approach to LDT regulation that focuses on tests with the greatest potential to cause harm—not a blanket regulation of all LDTs. We understand that greater regulation may be necessary for the small category of LDTs that provide profit-incentivized, direct-to-consumer tests with higher risks to the patient. However, as stated in previous sections, we disagree with the FDA's proposal to use the medical device risk classification system. Our concern lies in the FDA's approach to broadly regulate all LDTs by applying sweeping measures that do not align proportionately with the associated risk of the tests to patients.

   As noted, tests associated with a higher risk to the patient should be separately classified and may justify increased regulatory scrutiny. However, lumping all LDTs into a uniform regulatory framework, with the only differentiation being in timing of the enforcement discretion phaseout approach, is not a viable solution. For example, long-standing tests for therapeutic drug monitoring, established procedures that utilize accepted techniques that deliver excellent results with correlations to effective blood concentrations and compliance monitoring have been well-established for decades. There is no need to force laboratories to submit to 501k or a PMA to continue such testing.

2. **Allow existing LDTs to remain on the market without additional regulation.** The FDA asks whether the current enforcement discretion approach should be applied to tests already on the market, which is grandfathering of tests already in use. NILA and AAB support the grandfathering of LDTs currently in use, unless there are known adverse event reports surrounding those tests. Whatever solution is borne out by the rulemaking process must not be disruptive to patient care. Providers, clinicians, and patients rely on LDTs currently in use and are already under the enforcement discretion of the FDA.

3. **Allow third party reviewers:** The FDA does not currently have the capacity to regulate thousands of LDTs, which supports the suggestion to consider third-party partnerships to assist in review of high-risk LDTs. Specifically, the FDA is seeking comment on whether the New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP) or laboratory programs within the Veterans Health Administration may be "leveraged," meaning that LDTs under these programs would continue to be subject to enforcement discretion, and therefore exempt from the changes in the proposed rule.

   NILA and AAB support the use of third-party review and the use of other regulators to assist the FDA in the approval process for LDTs. The NYSDOH CLEP is an excellent example of a program that could be used by the FDA. Currently, the NYSDOH CLEP has approved thousands of LDTs under their regulatory structure. There may be other third-party reviewers who have, or will, establish similar approval processes. These should all be considered. We believe that if a test has already been through an adequate approval process, then the test should not have to be subject to a duplicative FDA approval process.

4. **LDT registration and adverse event reporting:** NILA and AAB appreciate that patients and practitioners want access to information about LDTs. For that reason, many community and regional clinical laboratories maintain electronic, internet-based test menus that include much of

the information sought by the FDA if the regulations were imposed to register an LDT. Overly detailed registration and listing requirements imposed on community, regional, and specialty laboratories would be extremely burdensome and duplicative of existing laboratory resources. **NILA and AAB recommend a limited registration requirement for existing tests and allowing laboratories to meet the requirements of registration and listing by maintaining an electronic, internet-based test menu on the laboratory's website and submitting the link to that test menu to the FDA.**

Conclusion

In conclusion, NILA and AAB members prioritize a patient-first approach in their work, emphasizing the importance of maintaining patient access to critical testing. Given the reasons outlined above, particularly, the drastic negative consequences this proposed rule will have on patient care, any authority to regulate LDTs should come from a clear mandate by Congress, rather than from the FDA. If Congress intends to further regulate LDTs, NILA and AAB recommend that the cost of these regulatory activities be federally funded. Lawmakers should avoid creating duplicative regulations and should consider a true risk-based framework for LDTs, especially those already established as safe and effective.

By minimizing duplicative and unnecessary barriers, especially for established LDTs that pose low risks to patients, NILA and AAB member laboratories can continue to provide patients and their health care providers with the tools to develop a diagnosis and treatment plan that works best for each unique case. The FDA must consider a balanced approach that encourages innovation, maintains accessibility, and understands the diverse landscape of laboratory testing. NILA and AAB's recommendations aim to provide a framework that addresses the FDA's concerns while ensuring LDTs continue to play a vital role in health care.

Sincerely yours,

Mark Birenbaum, PhD
Executive Director