November 29, 2023

Commissioner Robert Califf, MD
Dockets Management Staff (HFA-395)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Docket No. FDA-2023-N-2177 for Medical Devices; Laboratory Developed Tests

Dear Commissioner Califf:

The Association for Diagnostics & Laboratory Medicine (ADLM) welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) October 3, 2023, proposed rule, which would extend agency oversight to laboratory developed tests (LDTs). We have serious concerns about this proposal. If finalized, this rule would create a costly, dual regulatory structure limiting patient access to many life-saving tests.

ADLM recommends that the FDA withdraw FDA-2023-N-2177 and work with the laboratory community, patients, and Congress to update the Clinical Laboratory Improvement Amendments (CLIA) standards, the current mechanism for regulating these tests.

Legal Authority to Regulate LDTs
As the FDA is aware, there are legitimate questions about whether the agency has the legal authority to regulate LDTs. In 2015, distinguished jurists Paul D. Clement and Lawrence H. Tribe published a white paper arguing that the FDA was seeking to "*saddle a dynamic and innovative industry with sweeping new regulatory burdens without statutory basis*."[1]

Clement and Tribe further stated:

- *"Clinical laboratories have been regulated by the federal government in various ways, going back to at least 1967, and yet at no time was there any suggestion of the FDA's ability to regulate laboratory-developed testing services."*[2]

- *"The very enactment of the CLIA amendments in 1988 would be well-nigh inexplicable if Congress had intended in the 1976 MDA, as FDA asserts, to subject laboratory-developed testing services to the FDCA's device regulations."*[3]

[1] Paul D. Clement and Lawrence H. Tribe, *Laboratory Testing Services, As the Practice of Medicine, Cannot Be Regulated As Medical Devices*, January 2015.
[2] Ibid, page 15.
[3] Ibid, page 15.

- *"Indeed, neither CLIA's statutory text nor legislative history in 1988 makes any reference to preexisting FDA authority to regulate laboratory-developed testing services, let alone the sweeping authority to regulate such services as "medical devices."*[4]

Similarly, the Department of Health and Human Services (HHS) General Counsel echoed these concerns in its 2020 analysis of the FDA's legal authority to regulate LDTs. The counsel stated:

- *"the Agency's jurisdiction to regulate these devices is not uniform and not as plenary as it is for a traditional device."*[5]

- *"it appears likely that LDTs, even if they satisfy the constitutional and statutory "interstate commerce" requirements of the FDCA, would likely not satisfy the separate "commerce distribution" requirements of the premarket review provisions at sections 510(k) and 515."*[6]

- *Section 301(k), the primary provision dealing with prohibited acts, turns on whether the device is "held for sale." While the courts in the past have given that term a broad reading to include devices that never leave a physician's office, a plain meaning assessment may not be as agency friendly."*[7]

- *"many first-line sophisticated laboratories are operated by state public health departments or academic medical centers at large state universities. These laboratories, by definition, are not "persons," within the meaning of the Act, and not subject to many of the Act's requirements…"*[8]

ADLM suggests that FDA withdraw this proposal until a neutral arbiter can determine whether the agency has the authority to regulate these tests.

Legislative History

The FDA further claims throughout the document that Congress gave the agency authority to regulate medical devices dating back "to at least 1938"[9] and that test systems developed and sold by medical device manufacturers are the same as testing services provided by clinical laboratories; therefore, hospitals and commercial laboratories conducting such testing are manufacturers as well. While Congress has passed legislation giving the FDA authority over

[4] Ibid, page 15.
[5] Department of Health and Human Services Memo to FDA on the agency's legal authority to regulate LDTs, June 2022, page 2.
[6] Ibid, page 2.
[7] Ibid, page 2.
[8] Ibid, page 2.
[9] FDA Medical Devices; Laboratory Developed Tests proposed rule, October 3, 2023 *Federal Register*, page 68019.

the development and sale of test kits, the legislative authority to regulate testing services has been with the Centers for Medicare and Medicaid Services (CMS) and its predecessors.

- In 1965, Congress passed the Social Security Amendments Act, which created the Medicare and Medicaid programs. In 1966, the Social Security Administration (SSA) issued testing standards for clinical laboratories participating in the programs. These standards were enforced by the SSA and later the Health Care Financing Administration (HCFA)—the precursor to CMS.
- In 1967, Congress passed the Clinical Laboratories Improvement Act, which established separate standards for testing facilities engaging in interstate commerce. These rules were administered by the Centers for Disease Control (and Prevention) (CDC).
- In 1974, the Medicare/Medicaid and CLIA'67 programs adopted each other's standards, with the two programs later merging under HCFA (now CMS) oversight.
- In 1988, Congress passed CLIA'88, which unified and expanded the federal laboratory programs. HHS designated HCFA as the lead federal agency, which it has remained for the past 30 years.

FDA involvement in regulating testing performed in clinical laboratories has been at the periphery, at best. The legislative and regulatory history of laboratory testing supports CMS as the primary overseer of testing, not the FDA.

Cost-Benefit Analysis

The FDA's cost-benefit analysis of the proposed rule illustrates the need for gathering and evaluating additional data before any rule is advanced or action taken. As the FDA acknowledges, there are significant limitations in the data it used to conduct its regulatory analysis. Much of the information referenced by the agency is anecdotal or based on articles published in the popular press, not scientifically based evidence-driven studies. The result is a cost-benefit analysis that is so wide-ranging that it provides little meaningful insight into the impact of the proposed regulatory change. We are also concerned that the FDA is incorporating many flawed assumptions into its estimates.

According to the FDA, the annualized economic benefits from the proposal range from $2.67 billion to $86.01 billion over 20 years at a seven percent discount rate, whereas the annualized costs range from $2.52 billion to $19.45 billion over a similar period. The costs to the agency range from $265 million to $1.06 billion with a portion of this offset by user fees. These broad estimates reflect the agency's lack of information.

We are concerned that the agency is vastly overstating the benefits of greater oversight, while understating the direct and indirect costs to healthcare providers and patients, including the expenses associated with patients failing to have access to timely lifesaving diagnostic tests. One

industry analyst suggests the proposed rule will result in "a staggering $50 billion"[10] in costs to the laboratory industry over the first five years, while the suggested benefits are based on "highly speculative conjectures"[11] over 20 years.

ADLM believes that any analysis of LDTs must clearly delineate how many clinical laboratories will be affected and the number of LDTs that will be subjected to additional oversight. Further, the report must, at a minimum, address:

- the impact on the communities serviced by those clinical laboratories, with a special focus on the medically underserved individuals and vulnerable populations (e.g., children);
- the financial and resource costs of adopting the regulatory changes (e.g., hiring staff, generating required evidence, developing submissions, etc.); and
- the healthcare impact (e.g., decline in innovation, decrease in competition, patients unable to access tests, bad patient outcomes [increased disease-associated morbidity and mortality rates]).

These issues are not adequately addressed in the FDA economic analysis associated with the proposed rule. We recommend that an independent entity, such as the General Accountability Office, conduct such an analysis. Such a report should be provided to Congress for review and consideration prior to this proposal advancing.

The Central Importance of LDTs to Patient Care

LDTs of the 21st century play a critical role in providing quality patient care in the United States. These in-house developed tests are vital to screening and treating newborns for a myriad of genetic diseases, diagnosing and ensuring appropriate care for substance abuse victims, and minimizing organ rejection rate for transplant recipients. LDTs are also central to:

- detecting bacterial speciation for determining the appropriate antimicrobial drug therapy and eliminating the practice of administering broad-spectrum antibiotics, which is critical to reducing antibiotic resistance in the country;
- providing cellular and genetic cancer information that allows physicians to develop personalized treatment for patients; and
- determining if children have been exposed to lead, which can cause developmental delay (long-lasting cognitive impairment) if not treated earlier.

[10] Bruce Quinn, "*FDA Regulation of LDT's: The Hidden Facts You Need to Know*," October 10, 2023, page 3.
[11] Ibid, page 16.

This last example is a particularly good illustration of the vital rule LDTs play in providing the delivery of quality care. Lead exposure remains a significant public health crisis in the United States. The FDA has issued recalls for "LeadCare," blood lead test kits used at the point-of-care to rapidly assess blood lead concentrations. These recalls have affected hundreds of thousands of test results, primarily involving young children and women. It was only by sending the specimens to clinical laboratories that utilized definitive, LDT-based lead measurement that those affected were accurately diagnosed and treated.

Current Regulatory Structure

ADLM agrees that the increased number and complexity of LDTs may necessitate a review of the regulations governing these critically important clinical testing services. We believe, however, that the process for this review already exists within the CLIA regulations.

Administered by the CMS, CLIA provides a robust framework within which the agency oversees laboratory testing. CMS, with public input, created stringent federal standards that regulate laboratory testing, including LDTs. These standards include rigorous personnel, quality assurance, quality control, and proficiency testing requirements; regular inspections; and required corrective actions, when necessary.

In addition, many of the testing facilities that perform LDTs actively participate in the New York State, Joint Commission, College of American Pathologists (CAP), or other oversight programs, where they must meet requirements even more stringent than CLIA. ADLM is concerned that expanding oversight to include the FDA will divert limited laboratory resources from the provision of care to new, duplicative administrative requirements.

It is important to understand the differences in the roles of medical device manufacturers and clinical laboratories in providing testing services. Manufacturers develop the in vitro diagnostic (IVD) instruments and test kits sold to and used by a laboratory; medical laboratory professionals create LDTs to help physicians diagnose and treat patients when no comprehensive IVD product is available for a particular condition or purpose.

ADLM believes that any refinements to the regulation of LDTs be discussed and acted upon within the Clinical Laboratory Improvement Advisory Committee (CLIAC), which is the federal advisory body that guides CMS, FDA, and the CDC on changes to the CLIA policy. Changes beyond the scope of the panel should be addressed by Congress as part of a larger CLIA modernization effort.

FDA Proposed Regulatory Framework

The FDA states that laboratories that develop LDTs are medical device manufacturers and must be subject to the same requirements. The agency proposes to gradually end its general

enforcement discretion through five stages over four years. FDA would start by requiring laboratories to:

(1) meet medical device reporting requirements, including adverse events;
(2) meet certain premarket review and quality system standards;
(3) meet Quality System Regulation/Medical Device Good Manufacturing Practices requirements, as well as design and purchasing controls, among other changes; and
(4) meet premarket review rules for high-risk LDTs; and
(5) meet premarket review for moderate and low-risk tests.

FDA assumes that hospitals, small community testing facilities, and other providers can afford the technical and administrative staff necessary to perform the studies, file the submissions, provide supplemental information, and continue an ongoing dialogue with the FDA to gain agency clearance or approval of an LDT. We are concerned that the costs associated with this duplicative regulatory structure will be significant for many healthcare facilities, forcing them to discontinue or scale back these services. Rather than improving innovation and health equity, as the agency suggests, this proposal will do the opposite by limiting patient access to these vital tests.

Unintended Consequences of the FDA Proposed Rule

ADLM is concerned that the proposed rule will adversely affect the care provided to a wide spectrum of patient groups, particularly those in medically underserved populations, who will have less access, or delayed access, to these vital tests. LDTs are developed to fill a void—either a test kit is not available, the test kit on the market does not provide the information needed by the clinician, or the FDA-approved or cleared test is of limited diagnostic value. Listed below are just a few patient care areas that will be harmed by the FDA initiative:

Drug Testing

Substance abuse is a significant issue in the United States, contributing to numerous health problems, including liver disease, mental health disorders, and the spread of infectious diseases like HIV/AIDS and Hepatitis C through needle-sharing among intravenous drug users. In 2021, there were nearly 71,000 drug overdose deaths in the U.S. involving synthetic opioids, with a 22% increase from the previous year (2020) and synthetic opioids accounted for nearly 90% of opioid-involved deaths in 2021.[12]

Commercial diagnostic assays are typically based on workplace drug testing requirements and are not suitable for patient care because they report the classes of drugs present, not the specific drug taken. Medical laboratory professionals develop LDTs to identify the differing types of drugs (at low concentrations) so the physician can appropriately diagnose and treat the

[12] Centers for Disease Control and Prevention
https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm.

patient. Beyond the opioid epidemic, there is growing concern about the development and availability of new psychoactive substances (NPS). These substances, often referred to as "designer drugs" or "legal highs," have the same effect as illicit drugs while circumventing existing drug regulations.

It is important for clinical laboratories to have the needed flexibility to rapidly develop methods that detect these NPS. It is not clinically appropriate to wait for the development of commercially diagnostic assays, since these tests are often outdated by the time they are released. During that review phase, illicit drug manufacturers have already produced modified drugs to evade detection. LDTs are critical to diagnosing and treating these individuals.

A good example of this problem is the FDA-approved immunoassay drug screens for fentanyl. Most main chemistry analyzers using these assays are unable to detect fentanyl or any of its modified forms. LDTs are crucial to diagnosing and treating a person who has used this drug. If these LDTs are delayed by the regulatory pathways, when they are finally authorized or approved, they will already be obsolete because the relevant substances will have changed.

Pediatric Testing
Our pediatric population is one of our most vulnerable populations as they cannot advocate for themselves and often cannot communicate their clinical symptoms. Additionally, children are reliant on parents/guardians to coordinate their care, which is often complicated by work schedules, finances, and transportation challenges. Specialty care for children is also primarily available in large metropolitan areas, increasing the need to travel long distances for parents/guardians who care for children with complex health needs. An important example of this is NBS testing and follow-up.

NBS tests for inborn errors of metabolism (IEM) provide vital information for diagnosing and treating children with rare, often life-threatening, medical conditions. Although each individual disorder is rare, collectively it is estimated that one in roughly 2,000 newborns will have some sort of IEM. Phenylketonuria (PKU) is an example of a common inborn error of metabolism in which Children are unable to convert the amino acid phenylalanine to tyrosine due to a defective enzyme (phenylalanine hydroxylase).

If left untreated, the dangerous buildup of phenylalanine in the baby will result in devastating neurological symptoms, brain damage, and possibly death. However, children can lead normal, healthy lives by simply dietary modifications. Unfortunately, there are no FDA-approved tests to screen for or diagnose children with PKU or most other IEM. Screening tests like NBS are made very sensitive so no infant with the disorder will be missed. That sensitivity, however, results in a relatively high false positive rate. Thus, a positive NBS test must be confirmed by a second definitive test for the condition. <u>These confirmatory tests are all LDTs</u>.

Although the initial sample for NBS is collected while mother and baby are still in the hospital, confirmatory and follow-up testing are done as outpatients unless the infant is critically ill. Children's hospitals often have NBS follow-up testing in-house, allowing them to coordinate patient management in real-time with physicians and families who have traveled hours to have this testing performed. Any problems with specimen collection, results, and interpretations can be clarified and resolved on-site, preventing delay in treatment and diagnosis, numerous multi-hour trips or overnight stays which are a significant hardship to our patients, particularly those who live in rural settings and lack resources for travel and alternative local accommodations.

If these low-volume LDTs, which are well established and save many lives annually, were to require FDA submission – few hospitals would be able to continue to perform these tests. This would necessitate these in-house tests being sent to one or two central testing centers, requiring multiple days between specimen collection, and obtaining the results. The proposed rule may severely limit access to these life-saving tests for these children.

Molecular oncology

Another key area that could be adversely affected by the FDA proposed rule is the treatment of patients that have cancer. Broad molecular profiling of patient tumors by next-generation sequencing tests is standard of care in the diagnosis, prognosis, and therapy selection for patients that have cancer. Molecular testing in the realm of oncology encapsulates several methods that are commonly used to help pathologists reach a diagnosis, assist care teams to anticipate disease progression, and allow the physician and patient to select the therapeutic plan that minimizes toxicity. Few of these methods are in a pre-packaged, FDA-approved "kit" format, thus forcing clinical laboratories to develop these diagnostic tools locally. Furthermore, several drugs approved by the FDA over the last decade have no biomarkers of efficacy available beyond LDTs, including immune checkpoint inhibitor therapies such as pembrolizumab.

A key benefit of molecular profiling is the ability to simultaneously analyze hundreds of genes, decreasing the cost of testing and increasing patient safety because less tissue from invasive biopsies is required for NGS testing. Accelerating the pace of discovery in cancer research has been a national objective for decades, including the "Cancer Moonshot" initiative that emphasizes the need for advances in technology innovation, scientific discoveries, and therapeutic options. ADLM is concerned the duplicative FDA oversight of these tests will further limit the ability of healthcare providers to offer these tests. We are not averse to exploring additional ways to improve oversight of LDTs. However, any changes should take place through the congressionally mandated CLIA standards, of which the FDA is a partner with CMS and CDC.

Human Leukocyte Antigen Exemption

While LDTs are prominent in detecting exposure to illicit substances, they also ensure proper dosing of therapeutic medications. Important examples include antibacterial agents, antifungal agents, chemotherapeutic agents, and immunosuppressive agents like Tacrolimus, Sirolimus, and

Everolimus, which are used to prevent rejection and preserve the functionality of transplanted organs. These tests preserve transplanted graft function and save lives. The FDA proposes to exempt human leukocyte antigen testing as it is "generally performed, in urgent, life-saving situations for the patient."[13]

Although ADLM supports this exemption, it is unclear how the agency concluded that HLA testing is uniquely life-saving. There are many other life-saving LDTs, such as NBS assays, which are not exempted by the agency. For example, undetected deficiency of Medium Chain Acyl CoA Dehydrogenase (MCAD) deficiency in neonates has a mortality rate of 20-25%.[14] When part of a newborn screening protocol that is dependent on LDTs, this disorder has a mortality rate of less than 2%.[15] Why are these therapeutic and diagnostic tests not similarly exempt? The agency should more clearly specify the criteria for exempting categories of tests from expanded oversight.

The Need to Address Modified Tests

One frequently asked question is "what is an LDT?." While there is agreement that a test that is developed from scratch when no other test is available is an LDT, there are many tests that are designated as LDTs simply because the laboratory has made a slight modification to an FDA-approved test. Generally, this change is made (e.g., such as using a differing type of sample or modifying the stated stability of the sample) so that the lab can provide better service to their patients and obtain more specific and accurate information for the ordering provider.

For example, an FDA-approved test may call for a serum sample that is stable for one hour at room temperature. The lab's patient population may be over an hour away, so the lab performs a validation study that utilizes a dried blood spot sample, which is stable for 24 hours at room temperature, and gives the same result as the serum required by the test. ADLM believes that these types of test modifications that do not alter the clinical or analytical validity of the FDA-approved test should not be considered LDTs and or subject to additional regulation.

This point is especially important in the pediatric realm, where FDA-approved tests often are not validated using samples from pediatric patients. Further, it is important that all these tests not become LDTs simply because pediatric reference intervals are not in the Instructions For Use associated with the test system. Pediatric hospital labs will not be able to operate at all under these conditions, limiting patient access to testing and disrupting the delivery of healthcare. ADLM suggests that future discussions pertaining to LDTs address these tests. We think the following language would more narrowly define LDTs and exclude certain modified tests from additional, unnecessary regulation:

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[13] FDA Medical Devices; Laboratory Developed Tests proposed rule, October 3, 2023 *Federal Register*, page 68022.
[14] Wilson CJ et al. Arch Dis Child 1999; 80:459-462.
[15] Anderson DR et al Mol Genet Metab 2020;129:13-19.

"Clinical laboratories may modify an FDA cleared or approved test kit to meet a specific patient's need. If the modification does not change the assay itself, nor affect the manufacturer's clinical claims found in the test Instructions For Use (IFU), and the lab demonstrates that the modification does not adversely affect the analytic performance of the assay, the test is not an LDT and should not default to high complexity."

Need to Define the LDT Problem

One of the reasons for the greater LDT oversight, according to the FDA, is the quality of the testing. The agency makes this global statement without providing sufficient evidence to support its claim. The FDA frequently references anecdotal stories, news articles, FDA experience, and industry publications in support of its point. What is often lacking is sufficient evidence-based studies that support its position. In the past, when Congress asked the agency to provide supporting data it took two years to find twenty examples of tests that might be problematic—many of these claims were later disproven.[16]

One of the few studies the FDA references in the proposed rule was a 2022 paper -- *Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics* -- published in the *American Journal of Clinical Pathology*, which claimed the LDTs reviewed were inaccurate.[17] Yet, a more comprehensive study, *SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance*, published in *Archives of Pathology & Laboratory Medicine* reviewed the earlier analysis and, using the same samples, demonstrated that the LDTs in the study were in fact highly accurate.[18]

The FDA repeatedly references a January 1, 2022, New York Times article, *"When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong" in* support of expanded regulation of LDTs. Unfortunately, the agency fails to address the inaccuracies in the story, which mistakenly conflates screening and diagnostic tests as the same. The key takeaways from that story should be about the marketing techniques of some labs, and the need for physician education—issues the ADLM would agree need to be addressed--not the accuracy of LDTs.

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[16] Association for Molecular Pathology, December 13, 2015,
Facts FDA Ignored: An analysis of the FDA report, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies" https://www.amp.org/AMP/assets/File/position-statements/2015/AMPResponseFDACaseReportFinal.pdf?pass=64.

[17] Pfeifer, J.D., R. Loberg, C. Lofton-Day, et al., "*Reference Samples To Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics*," *American Journal of Clinical Pathology,* 157(4):628–638, 2022.

[18] Zehir A, Nardi V, Konnick EQ, Lockwood CM, Long TA, Sidiropoulos N, Souers RJ, Vasalos P, Lindeman NI, Moncur JT. SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance. Arch Pathol Lab Med. 2023 Sep 30. doi: 10.5858/arpa.2023-0322-CP. Epub ahead of print. PMID: 37776255.

ADLM is concerned that the agency is seeking to discredit a well-established form of testing, which is highly regulated, and provides accurate, vital information needed to diagnose, treat, and monitor many diseases. If the agency believes such testing is imperiling patient health, we urge the FDA to recommend that CLIAC place this on their agenda for immediate discussion, and they recommend that Congress hold hearings to explore the public health concerns and value of these tests.

The agency should not be seeking to take on the regulation of LDTs, where there is limited evidence of an existing problem.

FDA Resources

The FDA, by its own admission, is having problems hiring staff to meet its current responsibilities. Increasing this burden would add to the agency's problems, while potentially affecting patient care. The FDA's lack of resources to execute its existing mission was evident during the COVID pandemic when the agency had to limit the review of COVID Emergency Use Authorization tests to those with a volume greater than 500,000 per week. The inability of the FDA to review new COVID-19 tests raised legitimate concerns about whether the agency has the bandwidth to oversee LDTs, which could conservatively involve the review of tens of thousands of submissions.

For comparison, the Office of In Vitro Diagnostics, which would have oversight of LDTs, received a total of 112 510(k) submissions for the first recent quarter of this fiscal year and 10 PMAs.[19] It is clear the FDA does not have the staff nor resources to review many thousands of additional LDTs.

While ADLM believes that the FDA generally does a good job in evaluating new medical devices that enter the healthcare arena, its process is not perfect and, in fact, needs reform. There are many instances where test kits or drugs have been approved or cleared by the agency only to be later recalled. For example:

- In 2022, the FDA listed a recall relating to FDA-approved microbiologic susceptibility test plates – which help providers determine which drugs and doses are likely to yield clinical success in treating gram-negative bacterial infections in patients. The faulty plates had been in circulation for 22 months before the recall was released. The information shared with the FDA about the devices was self-disclosed on the part of the manufacturer after a single direct complaint and five medical device reports, consistent with Good Manufacturing Practice. The issue was only detected by clinical laboratory professionals as part of their own Good

[19] FDA Quarterly Update on Medical Device Performance Goals, MDUFA V CDRH Performance Data, Actions through 31 March 2023, 2nd Quarter FY 2023 MDUFA V Performance Report (fda.gov).

Clinical Practice measures, in compliance with *existing* regulatory compliance and oversight outlined by CLIA and enforced locally.

- In 2021, FDA-approved COVID-19 home tests were recalled after four months of availability on the market, when false-positive COVID results were reported. The recall was reported to the FDA by the manufacturer after 35 reports of false-positive test findings among users. Another manufacturer initiated a 2021 recall in its FDA-approved COVID PCR kit due to higher-than-expected rates of false *negative* results.

- In 2023, an FDA-approved cartridge-based test for myocardial injury was recalled more than six months after the test had been released to the clinical laboratory market. In this recall, the results were falsely low, increasing the risk of a missed diagnosis. There were 41 complaints to the manufacturer, and no injuries or deaths, which led to the reporting and recall of the devices.

We encourage the FDA to focus its attention on improving its existing review process, rather than seeking to add another area of responsibility that may hinder the agency's ability to meet its current workload.

Health Equity

The FDA states in the proposed rule that "increased oversight may help to advance health equity," through ensuring greater representation of marginalized populations in the clinical studies utilized in developing the test. The agency asserts this will increase the accuracy and usefulness of these tests.

ADLM is concerned that the agency is making policy based on speculative statements without providing scientific evidence to support these claims. Further, we share some of the concerns raised within the agency's cost-benefit analysis of the proposal regarding the potential impact of the proposed rule on underrepresented populations. The FDA analysis states:

"Nonetheless, while the proposed rule may help to advance health equity, we have no specific data showing that increased FDA oversight of IVDs offered as LDTs will necessarily reduce health disparities."[20]

"If laboratories pass-through the cost of compliance to the costs of IVDs offered as LDTs, testing frequency may decrease for areas that rely on IVDs offered as LDTs because of easy, rapid access."[21]

[20] FDA, Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, Unfunded Mandats Reform Act Analysis, Docket No. FDA-2023-N-2177, https://www.fda.gov/media/172557/download?attachment, page 105.
[21] Ibid, pages 105-106.

" If laboratories or healthcare facilities respond to increased compliance costs by increasing the price of IVDs offered as LDTs or reducing the availability of IVDs offered as LDTs, there may be an increase in health inequity."[22]

" Vulnerable populations that rely on IVDs offered as LDTs for diagnostic testing may have less access to diagnostic tests in general after the implementation of the rule."[23]

The agency should not be seeking to rush through a proposed rule that could have a deleterious effect on patient access to testing, particularly in economically and racially marginalized communities.

Exemptions
The agency is seeking input on those entities that should be exempt from FDA oversight. ADLM agrees that academic medical centers provide a unique service, conducting vital research, training healthcare personnel, and often serving marginalized and underserved populations. While we agree these institutions should not be subject to additional oversight, we believe exemptions do not necessarily need to be tied to the institution. CLIA high complexity laboratories performing LDTs should not be subject to additional oversight when:

- there is no FDA-approved test on the market; or
- an ordering physician determines the FDA-approved/cleared test is not appropriate for the patient's needs; or
- an ordering physician determines that a delay in testing could adversely affect patient care; or
- the individual performing the test is a trained medical laboratory scientist or qualified laboratory director under CLIA.

Adverse Event Reporting
The FDA wants to subject clinical laboratories performing LDTs to medical device reporting in phase one. ADLM does not believe the adverse event framework, which was developed for reporting problems involving medical devices, is appropriate for services provided by clinical laboratories. Results from LDTs do not generally result or contribute to the death or severe injury of a patient. During a January 2015 FDA Public Workshop on LDTs, the Mayo Clinic reported that over the previous five years, it had conducted more than 2.5 million LDT-based tests without a single sentinel event (The Joint Commission defines a sentinel event as a safety event that results in death or permanent harm to the patient).

One reason for the overall safety of LDTs is that laboratories implement internal quality controls that detect many analytical and pre-analytical errors and prevent inaccurate results from being

[22] Ibid, page 106.
[23] Ibid, page 106.

reported. The current CLIA regulatory framework also requires laboratories to identify, document, and perform corrective measures for any laboratory errors, and this would include errors resulting in patient harm if they were to occur. This documentation is reviewed on a regular basis by a CLIA inspector, its accrediting bodies or deemed state agencies. The current CLIA process could be modified to recommend that when a laboratory identifies a testing error it should report that mistake to the appropriate oversight body. This does not require legislative action.

User Fees

The proposal would create a new user fee program that would be applied to laboratories performing LDTs. Reimbursement for clinical laboratories is being cut dramatically under the Protecting Access to Medicare Act (PAMA), while at the same time, testing facilities must pay registration and accreditation fees under CLIA, as well as incur the costs of on-site inspections and frequent proficiency testing to demonstrate performance. The regulatory requirements outlined in this measure, along with the additional costs, would ensure that only a few laboratories would continue to offer LDTs. Unfortunately, this outcome would stifle innovation and harm patient care. ADLM believes that LDTs should remain under CLIA and that improvements should occur within the existing process established by Congress.

Thank you for the opportunity to provide input on the FDA's proposed rule to expand its oversight to include LDTs. If you have any questions, please email Vince Stine, PhD, ADLM's Senior Director of Government and Global Affairs, at vstine@myadlm.org.

Sincerely,

Octavia M. Peck Palmer, PhD, FADLM
President, ADLM