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Subj: ADLM Meeting with OMB OIRA regarding FDA Final Rule on LDTs

Dear Director Young, Administrator Revesz, & Associate Director for Health Spiro:

The Association for Diagnostics & Laboratory Medicine (ADLM) appreciates the Office of Management and Budget (OMB) Office of Information and Regulatory Affairs (OIRA) taking the time to meet with us to discuss the Food and Drug Administration's (FDA's) final rule to regulate laboratory developed tests (LDTs). While this final rule has not yet been released, this issue has been discussed within the healthcare community for more than a decade. ADLM thinks it is premature for OMB to release this rule, given:

- the legitimate concerns regarding the FDA's legal authority to regulate LDTs;
- the reasonable questions on whether the agency has adequately complied with the Administrative Procedures Act;
- the FDA's failure to properly assess the impact and costs of the rule;
- the duplicative nature of the rule given the Centers for Medicare and Medicaid Services (CMS) longstanding oversight of this area;
- the potential negative impact of the final rule on patient care, particularly populations with rare diseases, cancer, transplants, and novel infections; and
- the agency's lack of resources to implement the rule in a timely manner.

Legal Authority to Regulate LDTs

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 [Medical Device Amendments], as FDA asserts, to subject laboratory-developed testing services to the FDCA's [Federal Food, Drug, and Cosmetic Act] device regulations."*[3]

- *"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]

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[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.
[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.

- *"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 OMB direct FDA withdraw this rule 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 the development and sale of test kits, the legislative authority to regulate testing services has been with 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.

Administrative Procedures Act

The Administrative Procedures Act (APA) sets forth the criteria that federal agencies must employ when developing a rule. In its most basic format, the agency is required to develop a proposed rule, seek public comment on the proposal, review each comment, and then craft and promulgate a final rule that incorporates public feedback. The agency is directed to respond within that final rule to the public comments received.

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[8] Ibid, page 2.
[9] FDA Medical Devices; Laboratory Developed Tests proposed rule, October 3, 2023 *Federal Register*, page 68019.

For example, in February 2019, the Centers for Medicare and Medicaid Services published a proposed rule that would make modifications to its proficiency testing (PT) program under CLIA. It received 107 comments, which the agency responded in its July 2022 final rule. The estimated costs for implementing this final rule in 2022 ranged from $26 million to $94 million. CMS stated in the document that "generally, a final rule must be issued within 3 years of publishing a proposed rule, except under exceptional circumstances."[10]

ADLM is concerned that the FDA is not adequately following the process for developing a rule. It is unclear to us how the agency could finalize an extremely complicated, costly, and impactful proposed rule in less than three months, when it took CMS more than three years on a much less complex document with far fewer comments. The economic impact of the LDT rule, according to the FDA, could be as high as $86 billion (see below). That figure alone, if accurate, makes it extremely important that any regulatory action be comprehensive and precise, rather than fast.

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"[11] in costs to the laboratory industry over the first five years, while the suggested benefits are based on "highly speculative conjectures"[12] 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:

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[10] Centers for Medicare and Medicaid Services, *CLIA Proficiency Testing Regulations*, July 11, 2022, page 41194.
[11] Bruce Quinn, "*FDA Regulation of LDT's: The Hidden Facts You Need to Know*," October 10, 2023, page 3.
[12] Ibid, page 16.

- 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 urge you to review the comments submitted by ARUP Laboratories, which highlighted many mischaracterizations and inaccuracies in the FDA document. The regional laboratory, which is associated with the University of Utah stated that "*the FDA has made, at a minimum, an approximately 250-fold overestimate in its assessment of financial benefit*."[13]

As another commenter observed, the "*FDA's economic analysis systematically and repeatedly either understates the costs that will be imposed or ignores them altogether. Time and again, FDA simply does not mention entire categories of regulatory requirements that will apply to clinical laboratories. In order to meet its legal obligations, FDA must redo its cost analysis."*[14]

ADLM concurs with this assessment.

Current CMS Oversight 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

[13] ARUP Laboratories, November 28, 2023 comment to the FDA on FDA-2023-N-2177-0001, page 8.
[14] Hyman, Phelps & McNamara, PC, December 4, 2023 comments to the FDA on FDA-2023-N-2177-0001, page 26.

(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 should 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. Separate, duplicative FDA regulation is unnecessary and may harm patient care.

FDA Rule May Harm Patient Care

ADLM is concerned that the final 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 may be harmed if the proposed rule is finalized and promulgated:

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 newborn screening (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 with simple 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 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. Proposed FDA changes, if adopted, 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.

Marginalized Populations

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."[15]

"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."[16]

" 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."[17]

" 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."[18]

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.

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

[15] 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.
[16] Ibid, pages 105-106.
[17] Ibid, page 106.
[18] Ibid, page 106.

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 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 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.

The FDA should 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.

ADLM is a global scientific and medical professional organization dedicated to clinical laboratory science and its application to healthcare. ADLM brings together more than 50,000 clinical laboratory professionals, physicians, research scientists, and business leaders from around the world focused on clinical chemistry, molecular diagnostics, mass spectrometry, translational medicine, lab management, and other areas of laboratory science to advance healthcare collaboration, knowledge, expertise, and innovation.

[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).

On behalf of ADLM, I would like to thank you for the opportunity to engage OMB on this rule. If you have any questions, please email Vince Stine, PhD, ADLM's Senior Director of Government and Global Affairs, at vstine@myadlm.org.

Sincerely,

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