UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
SHERMAN DIVISION

AMERICAN CLINICAL LABORATORY ASSOCIATION, *et al.,* Plaintiffs,	)	
v.	)	Case No. 4:24-cv-479-SDJ
UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	)	
ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*, Plaintiffs,	)	
v.	)	Case No. 4:24-cv-824
UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	)	

BRIEF OF *AMICUS CURIAE* THE ASSOCIATION FOR ACADEMIC PATHOLOGY IN SUPPORT OF PLAINTIFFS

TABLE OF CONTENTS

STATEMENT OF THE INTEREST OF AMICUS 1

SUMMARY OF ARGUMENT 1

ARGUMENT 4

I. THE FDA'S NEW RULE WILL CAUSE UNNECESSARY PATIENT HARM AND DEATHS THAT DISPROPORTIONATELY IMPACT THE MOST VULNERABLE POPULATIONS AND EXACERBATES EXISTING PUBLIC HEALTH CRISES. 4

A. The FDA's new rule will harm millions of patients who rely on LDTs for accurate diagnoses and critical treatment. 4

B. The FDA's new rule will impede drug testing and further exacerbate the opioid epidemic and increase drug-related deaths. 6

C. The FDA's new rule will impede efforts to diagnose and treat certain cancers, delaying necessary and urgent care. 6

D. The FDA's new rule will disproportionately and adversely impact patients with rare diseases, delaying necessary and urgent care 8

E. The FDA's new rule will disproportionately and adversely impact pediatric patients, delaying necessary and urgent care. 8

F. The costs of seeking FDA approval will force AMCs to reduce or abandon LDT development, leaving the most vulnerable populations with diminished opportunities for treatment and recovery. 10

II. THE FDA'S NEW RULE WILL FRUSTRATE EFFORTS TO SWIFTLY CONTAIN AND MITIGATE EPIDEMICS AND PANDEMICS. 12

III. THE EXISTING REGULATORY REGIME UNDER THE CLINICAL LABORATORY IMPROVEMENT AMENDMENTS OF 1988 ("CLIA"), WITH APPROPRIATE MODIFICATIONS, ADEQUATELY PROTECTS PATIENT SAFETY. 13

A. Because LDTs are different from medical devices, they should not be regulated as medical devices 13

B. LDTs are already appropriately regulated to protect patient safety. 14

C. Individualized LDTs should be developed, administered, and overseen by experts, that is, clinicians, pathologists, and clinical laboratory scientists, and not FDA personnel. 17

D. Certain modifications or updates to CLIA may be necessary as medicine progresses. 18

CONCLUSION 18

TABLE OF AUTHORITIES

STATUTES

Clinical Laboratory Improvement Act Amendments of 1988, 42 U.S.C. §263a(a)..... 14, 15

Orphan Drug Act, 21 U.S.C. s360bb (1983)..... 8

RULES AND REGULATIONS

U.S. Centers for Medicare and Medicaid Services, Clinical Laboratory Improvement Act Amendments of 1988, 43 C.F.R. §§ 493.1200-1299 (Oct. 31, 1988) 15, 16

U.S. Food and Drug Administration, Medical Device User Fee Rates for Fiscal Year 2024—Notice, 88 Fed. Reg. 48, 870, 48, 873 (July 28, 2023) 11

U.S. Food and Drug Administration, Medical Devices; Laboratory Developed Tests—Final Rule (the "Final Rule"), 89 Fed. Reg. 37,286, 37,295 (May 6, 2024)..... 10

OTHER AUTHORITIES

Association for Academic Pathology, "About the AAPath," https://www.apcprods.org/ (last accessed Sept. 23, 2024) 1

George Washington University, "The Differences Between Academic and Community Medical Centers," (May 13, 2019), https://healthcaremba.gwu.edu/blog/the-differences-between-community-and-academic-medical-centers 2

Howard B. Fleishon, MD, MMa, *et al.*, "Academic Medical Centers and Community Hospitals Integration: Trends and Strategies," *Journal of the American College of Radiology,* Vol. 14, No. 1 (Jan. 2017)..... 2

Karen L. Kaul, M.D., *et al.,* "The Cause for Laboratory Developed Procedures: Quality and Positive Impact on Patient Care," *Academic Pathology*, Vol. 4: 1-21 (2017)..... 5, 7

Kimberly Proctor, "CMS Releases Data Briefs that Provide Key Demographic Data for the First Time," Centers for Medicare and Medicaid Services (July 25, 2023)..... 10

Letter from Association of Pathology Chairs to Commissioner Calif, re: "Response to Docket No. FDA–2023–N–2177 for 'Medical Devices; Laboratory Developed Tests,'" at 5 (Dec. 1, 2023).....11

Letter from Children's Pathology Chiefs to Commissioner Calif, re: "Comments Regarding the FDA Proposed Rule Titled 'Medical Devices; Laboratory Developed Tests,'" at 10 (n.d.) . 9, 10

Letter from the American Hospital Association to Commissioner Calif, re: "Docket No. FDA-20230N-2177; Medical Devices: Laboratory Developed Tests Proposed Rule (Vol. 88, No. 190), October 3, 2023" at 3-4 (Dec. 1, 2023).....3, 6, 11

Letter from the American Medical Association to Commissioner Calif, "Medical Devices; Laboratory Developed Tests—Docket No. FDA-2023-N-2177" at 2 (Dec. 4, 2023).....5, 11, 13

Letter from the Association of American Medical Colleges to Commissioner Calif, re: "Medical Devices; Laboratory Developed Tests (Docket No. FDA-20230N-2177) at 2 (Dec. 4, 2023).. 3, 8, 11, 16

Letter from the University of California to Commissioner Robert M. Califf, re: "Medical Devices: Laboratory Developed Tests" at 1-5 (Dec. 4, 2023)..... 7

Marilena Melas, *et al.*, "The Community Oncology and Academic Medical Center Alliance in the Age of Precision Medicine: Cancer Genetics and Genomic Considerations," *Journal of Clinical Medicine,* 9(7): 2125 (July 6, 2020)..... 7

Memo from R. Charrow (HHS) to S. Hahn (FDA) re Federal Authority to Regulate LDTs, at 102 (June 22, 2020)(the "Charrow Memorandum")..... 12

National Institutes of Health, "Rare Diseases," (Nov. 16, 2023), https://www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/promise-precision-medicine/rare-diseases . 8

National Institutes of Health, U.S. Overdose Deaths: Select Drugs or Drug Categories, 1999-2022, available at https://nida.nih.gov/sites/default/files/images/fig2-2024.jpg..... 6

Stanton L. Gerson, *et al.*, "Status of Cancer Care at Network Sites of the Nation's Academic Cancer Centers," *Journal of National Comprehensive Cancer Network*, 19(6): 726-732 (Mar. 11, 2021)..... 7

U.S. Food & Drug Administration, Report on Performance Goals for 2nd Quarter FY 2024, at 32, 124, 169 (May 31, 2024)..... 5

U.S. Substance Abuse and Mental Health Service Administration, 2023 NSDUH Annual National Report (July 30, 2024), available at https://www.samhsa.gov/data/report/2023-nsduh-annual-national-report..... 6

STATEMENT OF THE INTEREST OF AMICUS

Amicus the Association for Academic Pathology (AAPath) is a nonprofit, tax-exempt professional association that serves as the voice of academic departments of Pathology in the United States and Canada. AAPath exists "to provide leadership and advocacy for the dynamic discipline of Pathology and to enable academic departments to meet the demands of their three missions: medical education, research, and practice." Association for Academic Pathology, "About the AAPath," https://www.apcprods.org/ (last accessed Sept. 23, 2024). AAPath's members oversee patient care, clinical innovation, and teaching at hundreds of clinical laboratories directed by faculty in academic departments of pathology and laboratory medicine at academic medical centers (AMCs). AAPath academic faculty, including pathologists and Ph.D. clinical scientists, develop and administer laboratory developed tests (LDTs) and provide medical direction to clinical laboratory scientists who also conduct many of these tests. These medical professionals do not otherwise manufacture tests, devices, or kits that have historically been subject to Food and Drug Administration (FDA) regulatory oversight. AAPath's specific interest in this case relates to the impact of FDA's Final Rule on Medical Devices and Laboratory Developed Tests on AMCs as distinguished from industry.

SUMMARY OF ARGUMENT

The FDA Final Rule, as applied to AMCs, will greatly and adversely harm public health, disproportionately impact vulnerable populations, and frustrate efforts to swiftly respond to epidemics (e.g., the opioid epidemic) and pandemics (e.g., COVID-19, Monkeypox, SARS, etc.). AMCs are unique institutions in the United States healthcare system. Accounting for approximately 5% of U.S. hospitals, AMCs not only provide clinical care like their industry counterparts, but they also serve public health through the research and teaching missions of their

affiliated medical schools. George Washington University, "The Differences Between Academic and Community Medical Centers," (May 13, 2019), https://healthcaremba.gwu.edu/blog/the-differences-between-community-and-academic-medical-centers. To that end, in addition to providing time-sensitive, acute care to millions of patients annually across the spectrum of medical conditions, AMCs also "encourage innovation, research, and product development; identify and validate emerging care pathways; and provide education and training for the next generation of providers." Howard B. Fleishon, MD, MMa, *et al.*, "Academic Medical Centers and Community Hospitals Integration: Trends and Strategies," *Journal of the American College of Radiology,* Vol. 14, No. 1 (Jan. 2017).

Through mission-based service, AMCs connect clinical providers, pathologists, and Ph.D. clinical laboratory scientists to study and make advancements related to rapidly evolving diseases, including public health crises (e.g., the fentanyl epidemic, COVID, Monkeypox, etc.). Licensed and credentialed teams of professionals operate in highly regulated environments to create LDTs to diagnose and develop treatment plans for patients with routine and complex ailments alike. Especially with respect to confirmatory drug testing, certain cancers, rare diseases, pediatric conditions, and rapidly evolving diseases, customized LDTs are necessary for accurate and timely diagnosis and treatment. Whereas industry is more likely to be known for the development and mass production of commercial LDTs often distributed as kits (e.g., pregnancy tests, flu tests, allergen tests, UTI panels, etc.), LDTs at AMCs are not tangible products, but local processes and procedures used to diagnose disease, identify disease variants, confirm drug use, and more. Customized LDTs are necessary to timely and accurately diagnose and treat certain medical conditions. *See* Letter from the Association of American Medical Colleges to Commissioner Calif, re: "Medical Devices; Laboratory Developed Tests (Docket No. FDA-20230N-2177) at 2 (Dec. 4,

2023)(hereinafter, "AAMC Comment Letter") (Because "patients who come to academic medical centers . . . often require more tailored, specialized, or specific diagnostic tools….[t]he LDTs developed at academic medical centers seek to address pressing medical needs and complicated diagnoses for which their academic physicians require more information than can be gleaned from standard or commercially available tests."). Critically-ill patients cannot await FDA approval for necessary care.

While LDTs are used broadly to diagnose and treat routine medical conditions, a customized LTD may be created for use on a very small fraction of patients, such as adults suffering from rare diseases, cancer patients under consideration for precision medicine treatments, or children. AAMC Letter at 2. *See also* Letter from the American Hospital Association to Commissioner Calif, re: "Docket No. FDA-20230N-2177; Medical Devices: Laboratory Developed Tests Proposed Rule (Vol. 88, No. 190), October 3, 2023" at 3-4 (Dec. 1, 2023)(hereinafter, "AHA Comment Letter") (differentiating hospital/health system clinical laboratories, which typically develop LDTs in close collaboration with a clinical caregiver of a specific patient, from commercial and for-profit laboratories, which do not). LDTs in these small-scale or individualized contexts are not financially lucrative but are necessary for patient care. Under the FDA's new regulatory regime, the costs of obtaining regulatory approval will far exceed the costs of test development, forcing AMCs to shift costs to patients or discontinue critical care for persons with rare diseases, certain cancers, and children. These vulnerable populations will have nowhere to turn, as industry will not be inclined to invest human and financial resources for these individualized cases.

Finally, the FDA's regulations will essentially bar AMCs—which employ some of the most brilliant health care professionals and research scientists in the world—from assisting to mitigate

and contain existing and future epidemics or pandemics. Today, there are no FDA-approved confirmatory tests for fentanyl, and without the LDTs developed at AMCs, opioid-related deaths would have been considerably higher. Further, without the ability of AMCs to rapidly develop and use LDTs for future new illicit drugs, other overdose-related deaths will increase too, since the FDA new test approval time is much slower than the rate of appearance of new drugs (see below). This is troublesome since illicit drug use impacts one-sixth of the U.S. population annually. Further, the FDA's new rule will frustrate efforts to contain and mitigate the next global pandemic, as evidenced by data points from the COVID-19 pandemic.

Whether discussing acute care for routine diseases, opioid overdoses, rare diseases, cancer, pediatric care, or unmitigated pandemics, it is not an exaggeration to predict that adults and children alike will experience harm, including death, due to the FDA's *ultra vires* action. The existing regulatory regime, with modifications to reflect medical and scientific advancements, more than adequately protects patient safety and best serves public health.

ARGUMENT

I. THE FDA'S NEW RULE WILL CAUSE UNNECESSARY PATIENT HARM AND DEATHS THAT DISPROPORTIONATELY IMPACT THE MOST VULNERABLE POPULATIONS AND EXACERBATES EXISTING PUBLIC HEALTH CRISES.

A. The FDA's new rule will harm millions of patients who rely on LDTs for accurate diagnoses and critical treatment.

LDTs are customized analytical processes that are created by pathologists, clinical laboratory scientists, and Ph.D. scientists, each of whom has highly specialized knowledge both in the analytical process underlying a specific testing procedure and, in many instances, the unique condition of the person or persons needing the testing. LDTs are used for routine testing on *millions* of patients (e.g., automated immunohistochemistry, flow cytometry, mass spectrometric drug analyses, microorganism culture and sensitivities). In many instances—especially at AMCs—

LDTs are customized to a patient's unique circumstances (age, symptoms, environment, etc.). For example, multi-drug-resistant infectious organisms create unique diagnostic, therapeutic, and prognostic issues, particularly in immunocompromised patients, and when these medical conditions present, customized LDTs are necessary for a timely and accurate diagnoses and urgent treatment.

Timeliness and urgency are antithetical to the FDA's regulatory approval process, which will inevitably delay critical, and, in some instances, life-saving care. A typical FDA review takes an average of 451-58 days, depending on the type of review necessary. U.S. Food & Drug Administration, Report on Performance Goals for 2nd Quarter FY 2024, at 32, 124, 169 (May 31, 2024). Quite simply, a patient with an aggressive disease cannot wait 451 days for FDA approval before a diagnosis is confirmed and a treatment plan is initiated. *Cf.* Letter from the American Medical Association to Commissioner Calif, "Medical Devices; Laboratory Developed Tests—Docket No. FDA-2023-N-2177" at 2 (Dec. 4, 2023)(hereinafter, "AMA Comment Letter").

Highly trained pathologists and laboratory professionals must be empowered to swiftly and nimbly devise and administer individually tailored LDTs to diagnose disease so that patients can receive urgent, necessary, and, in some instances, life-saving treatment. *See* Karen L. Kaul, M.D., *et al.,* "The Cause for Laboratory Developed Procedures: Quality and Positive Impact on Patient Care," *Academic Pathology*, Vol. 4: 1-21 (2017) ("Pathologists and laboratory professionals need the best and most up-to-date tools to do their jobs and optimize patient care."). Absent the ability to develop such individualized tests, doctors—and, by extension, their patients—will need to rely on sub-optimal existing tests that are generic, imprecise, less-accurate, and ignorant of the patient's unique condition. *See* AHA Comment Letter at 3-4 (The FDA's regulatory regime will "harm patient access to the most advanced diagnostics."). While industry may be able to pay the costs

and weather the delays of awaiting FDA approval for a mass-produced flu swab or other similar commercially available tests, AMCs cannot absorb the costs, and critically ill patients cannot await delays, sometimes literally, as they may experience serious harm or die while awaiting FDA review.

B. The FDA's new rule will impede drug testing and further exacerbate the opioid epidemic and increase drug-related deaths.

The FDA's new rule will impede confirmatory drug testing, increase fentanyl deaths, and exacerbate the opioid epidemic. Nearly 48 million people in the United States used an illicit drug in the past month. U.S. Substance Abuse and Mental Health Service Administration, 2023 NSDUH Annual National Report (July 30, 2024), available at https://www.samhsa.gov/data/report/2023-nsduh-annual-national-report. Of those who use illicit drugs, 8.9 million people misuse opioids, and 75,000 people die each year in the United States from a fentanyl overdose. National Institutes of Health, U.S. Overdose Deaths: Select Drugs or Drug Categories, 1999-2022, available at https://nida.nih.gov/sites/default/files/images/fig2-2024.jpg. Other than LDTs, there currently exists no confirmatory test for fentanyl or any of its numerous analogues that are not LDTs. Without LDTs, fentanyl deaths will rise, further exacerbating the opioid epidemic. More broadly, physicians will be unable to conduct confirmatory drug testing to prevent overdose deaths, unnecessarily exacerbating a public health crisis that personally affects one-sixth of the U.S. population.

C. The FDA's new rule will impede efforts to diagnose and treat certain cancers, delaying necessary and urgent care.

Customized LDTs are critically important for cancer diagnosis and treatment. *See* Karen L. Kaul, M.D., *et al.,* "The Cause for Laboratory Developed Procedures: Quality and Positive Impact on Patient Care," *Academic Pathology*, Vol. 4: 1-21 (2017); Letter from the University of

California to Commissioner Robert M. Califf, re: "Medical Devices: Laboratory Developed Tests" at 1-5 (Dec. 4, 2023)(illustrating how LDTs have traditionally been used in cancer diagnosis and treatment). As one example, immunohistochemical (IHC) stains are LDTs and a long-standing mainstay of cancer diagnosis and treatment planning. IHC stains help to distinguish one type of cancer from another, for example, by identifying a primary cancer in a patient with metastasis. LDTs are also used in this context to identify an individually-tailored treatment. For example, in breast cancer, IHC staining for estrogen and progesterone receptors has been done with success for decades and determines whether a patient will receive hormonal therapy or not. In more recent times, IHC stains help determine whether a patient is a candidate for immunotherapy, a transformative therapy for many cancers. Cancer genetics and genomics tests are created and offered as LDTs at AMCs to advance precision medicine treatments for cancer. AMCs are increasingly associated with networks involving community hospitals to bring these leading-edge treatments to support local cancer care in small and rural communities. Marilena Melas, *et al.*, "The Community Oncology and Academic Medical Center Alliance in the Age of Precision Medicine: Cancer Genetics and Genomic Considerations," *Journal of Clinical Medicine,* 9(7): 2125 (July 6, 2020); Stanton L. Gerson, *et al.*, "Status of Cancer Care at Network Sites of the Nation's Academic Cancer Centers," *Journal of National Comprehensive Cancer Network*, 19(6): 726-732 (Mar. 11, 2021). Timely and individualized diagnosis and treatment are critical to treating and managing cancer which can mitigate or prevent metastasis or cancer-related complications. The FDA's aggressive regulatory scheme will again, delay access to care, and cause unnecessary harm, including deaths.

D. The FDA's new rule will disproportionately and adversely impact patients with rare diseases, delaying necessary and urgent care

Rare diseases affect between 25 million and 30 million Americans. National Institutes of Health, "Rare Diseases," (Nov. 16, 2023), https://www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/promise-precision-medicine/rare-diseases. While both industry and AMCs provide valuable and necessary health services to patients and communities, AMCs, driven, in part, by the research and teaching missions of the affiliated medical schools, connect highly trained clinicians, pathologists, and Ph.D. clinical laboratory scientists to study and make advancements in the field of rare diseases. *See* AAMC Comment Letter at 6. Sometimes, the diseases are ones of first impression, impacting only a single-known individual. Other times, they are "orphan diseases," or diseases that only impact a small portion of the population. Orphan Drug Act, 21 U.S.C. s360bb (1983). Only about 500 rare diseases (between 5-7% of rare diseases) have FDA-approved treatments. National Institutes of Health (NIH), "Rare Diseases" (Nov. 16, 2023). Efforts to study and cure the remaining 93%-95% of rare diseases are born purely from AMCs' educational and humanitarian missions, and not from financial promise, as similar efforts on behalf of such a small population would not serve the business interests of the for-profit industry. To be clear, LDTs in such individualized contexts are not financially lucrative and thus will not be produced by industry. The costs of obtaining regulatory approval will far exceed the costs of test development, forcing AMCs to employ sub-optimal tests, shift costs to patients, or discontinue critical care for persons with rare diseases.

E. The FDA's new rule will disproportionately and adversely impact pediatric patients, delaying necessary and urgent care.

AMCs disproportionately treat pediatric patients because children's hospitals are often located at AMCs. Letter from Children's Pathology Chiefs to Commissioner Calif, re: "Comments

Regarding the FDA Proposed Rule Titled 'Medical Devices; Laboratory Developed Tests,'" at 10 (n.d.). As with all AMCs generally, these research-focused pediatric care centers specialize in serious illnesses and complex chronic conditions, many of which present as rare or orphan diseases. *Id.* at 1-2. Because existing diagnostic tools and treatments that are developed for adult populations do not take into account the unique issues in various pediatric reference ranges, LDTs are needed to "fill a critical gap in the practice of pediatric medicine as they allow for accurate, timely, accessible, and high-quality testing for many pediatric conditions for which no commercial test exists or where an existing test does not meet current critical needs." *Id.* For this very reason, LDTs are used more frequently at children's hospitals relative to adult-centered hospitals.

The reason LDTs are used so frequently in pediatrics is because children present unique technical challenges that make pediatric testing different and more difficult than adult testing. As explained by the Children's Pathology Chiefs,

> [T]esting for pediatric patients face challenges unique to sample collection, sample volumes and test reference (normal) ranges that could account for the full range of human growth and development. LDTs allow [treating clinicians] to make needed technical changes to serve pediatric patients, like expanding reportable range, changing reference intervals, or changing interference tolerance.

Id. at 6. In other words, diagnostic and treatment decisions related to children must account for age and various stages of development (e.g., lung capacity, hormone levels, etc.). This requires individualized treatment and again, make these kinds of necessary and life-saving LDTs unappealing to for-profit industry. Just as with the diagnosis and treatment of rare diseases, the "market financial gains [for the development of diagnostic pediatric tests] are too small for larger manufacturers to justify." *Id.* at 3.

As a last point, Medicaid is the largest insurer for children in the United States. *Id.* at 8. Disproportional reliance on Medicaid strains budgets at children's hospitals, presenting yet another barrier to compliance with the FDA's new rule. *Id.* at 8. Children's hospitals will be forced to abandon or reduce LDTs, which will have devastating consequences on the diagnosis and treatment of childhood illnesses, and which will inevitably result in preventable harm and premature child deaths. Finally, because children from minoritized backgrounds are more likely to be enrolled in Medicaid, the resulting consequences of the Final Rule's implementation will be disproportionately borne by minoritized communities, accentuating existing health inequities. *Id.* at 10. *See also* Kimberly Proctor, "CMS Releases Data Briefs that Provide Key Demographic Data for the First Time," Centers for Medicare and Medicaid Services (July 25, 2023)("[T]he [Medicaid] programs' enrollees were more racially and ethnically diverse than the broader U.S. population. These findings are particularly pronounced for children, with 61 percent of child enrollees in 2020 being from racial and ethnic minority backgrounds.").

F. The costs of seeking FDA approval will force AMCs to reduce or abandon LDT development, leaving the most vulnerable populations with diminished opportunities for treatment and recovery.

AMC laboratories do not have sufficient human or financial resources to continue existing diagnostic practices that are now subject to FDA regulation. The costs of seeking FDA approval will far exceed the costs of test development, leading to an inevitable overall decline in LDTs. The FDA estimates that filing submissions will range from $530,410 on the low end, to $9.29 million for more high-risk devices. FDA, Medical Devices; Laboratory Developed Tests—Final Rule (the "Final Rule"), 89 Fed. Reg. 37,115, 37,123 (May 6, 2024). In addition, applicants must pay a "user fee" which could be as high as $483,560. FDA, Medical Device User Fee Rates for Fiscal Year 2024—Notice, 88 Fed. Reg. 48, 870, 48, 873 (July 28, 2023). Quite simply, AMCs will not be able

to absorb these costs and will either be forced to pass costs onto patients or forego necessary research and development. Indeed, in a recent survey conducted by AAPath of its members, 90% of laboratories anticipated that once the FDA final rule becomes final, they would need to indefinitely remove LDTs from their test menus to await commercial options. Letter from Association of Pathology Chairs to Commissioner Calif, re: "Response to Docket No. FDA–2023–N–2177 for 'Medical Devices; Laboratory Developed Tests,'" at 5 (Dec. 1, 2023). The American Medical Association echoed this finding in its December 4, 2023 comment letter to Commissioner Califf, noting that "laboratories of all types . . . will likely have to significantly reduce their test offerings should these types of regulatory requirements go into effect" which is expected to result in "a substantial decrease in access to diagnostic testing services." AMA Comment Letter at 9. *See also* AHA Comment Letter at 3-4 ("Imposing these additional costs and burdens is untenable and would ultimately lead to institutional decisions that would limit the types and number of LDTs offered by the institution, leading to a substantial reduction in patient access to innovative and targeted diagnostic tests."); AAMC Comment Letter at 7 ("[A]cademic medical centers [will] be forced to make decisions about which FDA applications [will] be assembled and submitted, and which tests [will] instead be abandoned or not development, to the detriment of patients that could benefit from them."). Even well-funded AMCs that are able to continue operations will almost assuredly be forced to reduce the scale of LDT use, necessarily having to reassign staff to administrative functions necessary for FDA approval when they could be developing and administering a novel, life-saving test. Finally, that the regulations have taken effect amidst a national laboratory workforce shortage compounds the adverse effect and increases the likelihood of harm.

II. THE FDA'S NEW RULE WILL FRUSTRATE EFFORTS TO SWIFTLY CONTAIN AND MITIGATE EPIDEMICS AND PANDEMICS.

The FDA's new rule will frustrate efforts to swiftly contain and mitigate epidemics and pandemics. This proposition is hardly theoretical and instead reflects actual events in early 2020, at the start of the COVID-19 pandemic. In the early days of the pandemic, while the world was sheltering in place awaiting information about an unknown disease that was killing an unusually large percentage of the population, AMCs stayed open, both to continue research and development efforts and treat very ill patients. Under CLIA, AMCs normally would have been able to develop and administer COVID tests that reliably detected the virus and helped prevent its spread. There would have been robust information sharing among AMC laboratories to initiate the widespread development of precise and accurate LDTs to diagnose COVID-19 and its variants, all in the interest of public health.

However, the FDA was already exercising *ultra vires* authority by endeavoring to regulate without appropriate notice and comment rulemaking on a matter outside of its jurisdiction. Specifically, without having been granted Congressional authority to regulate LDTs, the FDA deemed LDTs created pursuant to HHS's Emergency Health Declaration (e.g., COVID tests) to be "higher risk" than other LDTs, and sought information from AMCs on the "design, validation, and performance characteristics" of these LDTs. Memo from R. Charrow (HHS) to S. Hahn (FDA) re Federal Authority to Regulate LDTs, at 102 (June 22, 2020)(the "Charrow Memorandum"). This regulatory flex caused AMCs to pause research and development on COVID-19 tests. This left the world with inadequate information to diagnose COVID-19. Medical centers were overrun with patients who unknowingly contracted the virus from asymptomatic peers, emergency rooms became backlogged, the pandemic spread, and unnecessary casualties resulted.

Eventually, the Charrow Memorandum was rescinded, and allowed, as pointed out in the complaint, "the first valid procedures for distinguishing the SARS-COV-2 virus from more benign respiratory illnesses were developed as LDTs in clinical laboratories." Compl. ¶ 106. But the damage had already been done as evidenced by the initial uncontrolled spread and resulting casualties and economic consequences from which the world is still recovering.

The FDA's new regulatory regime repeats this mistake, and, for that reason alone, the rule has significant political and economic consequences in addition to the human consequences. Rather than vesting AMCs' experts with necessary discretion to act swiftly to contain a public health crisis, the new rule formalizes the exact problems identified in the Charrow Memorandum via regulation, perplexingly diluting the nation's ability to mitigate the next COVID, AIDS, Zika, Ebola, MonkeyPox, or other unknown virus. Pandemics are among the many examples of urgent situations in which deregulation best serves the public health, serves the economy, and most importantly, saves lives. *See* AMA Comment Letter at 2 ("[E]arly diagnostic development is of critical importance to protect our patients during times of an emergency public health crisis.").

III. THE EXISTING REGULATORY REGIME UNDER THE CLINICAL LABORATORY IMPROVEMENT AMENDMENTS OF 1988 ("CLIA"), WITH APPROPRIATE MODIFICATIONS, ADEQUATELY PROTECTS PATIENT SAFETY.

A. Because LDTs are different from medical devices, they should not be regulated as medical devices.

LDTs as customized analytical processes that are often individualized for a unique condition of the person or persons needing the testing are distinct from medical devices. Unlike medical devices, these testing services are not tangible products but processes and procedures which require human intervention from highly trained licensed and board-certified specialists to

design, calibrate, perform, and interpret the tests in an already highly-regulated laboratory. Medical devices, on the other hand, are mass produced and commercially distributed as a product on a large-scale basis to patients and providers. They are not individually tailored—every bionic knee manufactured by X industry in X year is the same. Further, it is almost assured that an engineer or someone else outside of the medical field is creating the medical device, as opposed to the trained and highly specialized clinicians and scientists who develop and administer LDTs in AMC laboratories. While it makes sense that 100,000 identical pacemakers created by a non-medically trained engineer should require FDA approval, it does not make sense that each of 100,000 different and individualized tests created by highly trained and specialized pathologists, clinical laboratory scientists, and Ph.D. scientists in AMC clinical laboratories, each of whom has unique knowledge about a patient's individualized circumstances, would require FDA approval.

B. LDTs are already appropriately regulated to protect patient safety.

LDTs are already appropriately regulated under CLIA and other regulatory, accreditation, and licensing regimes that overlay with CLIA. CLIA is a comprehensive regulatory regime that certifies "laborator[ies] or clinical laborator[ies]" to examine "materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings." 42 U.S.C. §263a(a). To obtain certification, a laboratory must first submit information regarding (i) the number and types of laboratory examinations and other procedures performed, (ii) the methodologies for laboratory examinations and other procedures performed, and (iii) the qualifications (educational background, training, and experience) of the personnel directing and supervising the laboratory and performing laboratory examinations and other procedures. *Id.* § 263a(d)(1)(A). Certified laboratories must comply with various standards established by the Secretary of Health and Human

Services, which include requirements that each laboratory (A) "maintain a quality assurance and quality control program adequate and appropriate for the validity and reliability of the laboratory examinations and other procedures of the laboratory and to meet requirements relating to the proper collection, transportation, and storage of specimens and the reporting of results"; (B) "maintain records, equipment, and facilities necessary for the proper and effective operation of the laboratory," (C) employ qualified and specialized personnel to perform and carry out laboratory examinations and other procedures, and (D) qualify under a proficiency testing program meeting the HHS standards and "to meet such other requirements as the Secretary determines necessary to assure consistent performance by such laboratories of accurate and reliable laboratory examinations and procedures." *Id.* § 263a(f)(1). These statutory standards are uniquely tailored to each laboratory insofar as the legislation directs the Secretary to consider

> (A) the examinations and procedures performed and the methodologies employed,
> (B) the degree of independent judgment involved,
> (C) the amount of interpretation involved,
> (D) the difficulty of the calculations involved,
> (E) the calibration and quality control requirements of the instruments used,
> (F) the type of training required to operate the instruments used in the methodology, and
> (G) such other factors as the Secretary considers relevant.

Id. §263a(f)(2). All laboratories are subject to surprise compliance inspections and face significant penalties for noncompliance. *Id.* §263a(g).

More than that, CLIA's implementing regulations require measures for "quality, validity, reliability, and accuracy of every laboratory procedure performed in a certified and accredited laboratory, including for every individual LDT." *See* 43 C.F.R. §§ 493.1200-1299. LDT processes and procedures must be memorialized in a written procedural manual that includes very detailed and specific regulatory requirements, *id.* §493.1251; the lab must establish and verify performance specifications, *id.* §493.1253; the lab must perform routine maintenance and function checks, *id.*

§493.1254; the lab must implement calibration and calibration verification procedures, *id.* §493.1255; and the lab must implement "control procedures that monitor the accuracy and precision of the complete analytic process," *id.* §493.1256a.

In addition to the CLIA regulatory regime, AMC laboratories are subject to a higher level of oversight than commercial laboratories. AAMC Comment Letter at 3. For example, many AMCs are located in teaching hospitals and must meet Joint Commission standards, which includes laboratory accreditation by the Joint Commission or other agencies that have been deemed acceptable, such as the College of American Pathologists. Finally, grafted onto the already onerous regulatory regime and accreditation process are the rigorous educational and licensure requirements for pathologists, clinical laboratory scientists and Ph.D. clinical scientists. Each of these professionals must be certified via rigorous educational requirements and testing, and deemed by experts in the field to be highly qualified within their respective fields. While the tens of thousands of existing LDTs may not each be individually regulated, the environment in which they are created and implemented is *highly* regulated.

The FDA has used anecdotes to stoke displaced fear about safety. They've pointed to false positive results in Lyme Disease testing, when the false positive result was only .016%, a percentage well within accepted margins of error within the medical community. The FDA has pointed to alleged errors in ovarian cancer screening and detection, when the allegations were based on tests performed outside of the United States (and thus not subject to the CLIA regulatory regime) or disputed data that awaits confirmation in a larger study. The FDA also points to alleged errors that would not be remedied by requiring FDA approval of tests because the errors derived from pre- or post-test human error. For example, human error could result in the wrong test being ordered or the results being misinterpreted. It is not disputed that these kinds of errors happen, but

the appropriate and complex question here is (1) whether FDA oversight would have eliminated the errors and (2) even in the very few circumstances where FDA oversight *may* have eliminated the errors, whether more lives would be saved by instead vesting pathologists and other laboratory professionals with the necessary discretion to provide diagnostic tests and vesting treating clinical providers with the discretion to order and use these tests to treat serious and life threatening ailments in a timely and medically necessary manner. The FDA's anecdotes are disingenuous and calculated to stoke unnecessary fear. The greater fear should be the medical harm, including lives lost, after the FDA's regulatory regime is implemented.

C. Individualized LDTs should be developed, administered, and overseen by experts, that is, clinicians, pathologists, and clinical laboratory scientists, and not FDA personnel.

Persons with serious or rapidly progressing medical illnesses, including cancer and rare diseases, as well as children face few options. Oftentimes, the kinds of LDTs developed and administered at AMCs are individualized processes tailored to unique clinical and diagnostic circumstances. Pathologists, clinical laboratory scientists, and Ph.D. clinical scientists have the requisite knowledge, expertise, and professional relationships with clinical providers to tailor appropriate LDTs to specific patient needs. An FDA employee does not have the same breath, depth of expertise, and individualized patient relationship to determine the clinical relevance and necessity, across the spectrum of medical specialties, to "approve" and LDT in any way that would reasonably advance public health or patient safety. With the existing regulatory guardrails that are already in place, and without the same financial incentives that drive industry and create conflicts of interest, LDTs should be overseen by medical experts who have a professional duty to patient care, not political or career appointees with little or no medical training and *no* knowledge of a patient's unique circumstances.

D. Certain modifications or updates to CLIA may be necessary as medicine progresses.

Few, if any, federal regulations remain static over time, and that is especially true in fields like science, engineering, and technology, where discoveries and advancements change the field in unpredictable ways. While *amicus* believes that CLIA provides a sound architecture for appropriate regulatory oversight of LDTs, *amicus* acknowledges that updates and modifications may be necessary as the field evolves. As one example, as artificial intelligence (AI) becomes more integrated into medicine, the Center for Medicare and Medicaid Services, the regulatory body that enforces CLIA, may wish to address the use of AI in diagnostic testing. AAPath as *amicus* is cognizant that thoughtful and carefully tailored regulatory updates or modifications may serve the public interest, though the FDA's existing *ultra vires* rule does not.

CONCLUSION

The FDA's new rule, as applied to AMCs, has great political, economic, and human consequence. It will cause patient harm, including unnecessary deaths. It will harm public health and frustrate the ability to contain and mitigate pandemics and epidemics (both existing epidemics such as the opioid crisis and global pandemics like COVID), again prompting unnecessary illness, deaths and catastrophic economic consequences. The existing regulatory regime under CLIA, with appropriate and tailored modifications to address evolving science, adequately protects public safety and best serves human interests.

Respectfully submitted,

/s/

Holly E. Peterson
Counsel

Tenenbaum Law Group PLLC
610 13th Street NW, 12th Floor
Washington, DC 20005
Tel. (202) 221-8006
Fax (202) 221-8001
hpeterson@tenenbaumlegal.com

Admitted *pro hac vice*
Maryland Bar No. 1206200049

Counsel for *Amicus Curiae*

CERTIFICATE OF SERVICE

I hereby certify that on October 7, 2024, this document was filed through the Court's CM/ECF system, which served it upon all counsel of record. Dated: October 7, 2024.

Respectfully submitted,

/s/

Holly E. Peterson
(Admitted *pro hac vice*)