UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
SHERMAN DIVISION

AMERICAN CLINICAL LABORATORY ASSOCIATION; HEALTHTRACKRX INDIANA, INC.; and HEALTHTRACKRX, INC., Plaintiffs, v. U.S. FOOD AND DRUG ADMINISTRATION; U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services; and ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, United States Food and Drug Administration, Defendants.	**DECLARATION**

DECLARATION OF JONATHAN GENZEN, M.D., Ph.D.

I, Jonathan Genzen, M.D., Ph.D., declare as follows:

1. I am a resident of Salt Lake City, Utah. I am over the age of eighteen, and I am competent to provide this declaration.

2. I am the Chief Medical Officer and Senior Director of Government Affairs at ARUP Laboratories and have served in these roles since July 2022.

I am also the Medical Director of Laboratory Automation for ARUP Laboratories and a Co-Medical Director of Automated Core Laboratory at ARUP Laboratories.

3. I have worked at ARUP Laboratories for more than 11 years.

4. In addition to my work at ARUP Laboratories, I am a clinical Professor in the Department of Pathology at the University of Utah School of Medicine. I am licensed to practice medicine in both Utah and New York.

5. I received my Ph.D. in Biological Sciences at the University of Chicago and my M.D. in Medicine at the University of Chicago Pritzker School of Medicine.

6. I completed my clinical pathology residency training at Yale University / Yale New Haven Hospital, and I was a post-doctoral Research Fellow at Yale University in the Department of Laboratory Medicine.

7. I specialize in clinical pathology, laboratory medicine, clinical chemistry, medical diagnostics, in vitro diagnostics, and laboratory automation.

8. I am a fellow of the American Society for Clinical Pathology and the College of American Pathologists. I am also a member of the Association for Diagnostics and Laboratory Medicine and the Academy of Clinical Laboratory Physicians and Scientists.

9. As a result of my professional experiences and background, I have significant knowledge of clinical diagnostic laboratory services. I am familiar with the legal and regulatory requirements that have long applied to laboratory-developed tests, including the regulations that apply to the conduct of laboratories and the validation of diagnostic testing services.

10. I am also familiar with the final rule issued by the Food and Drug Administration ("FDA") on May 6, 2024, and the analysis that the FDA has relied on to justify its new rule. I was directly involved in preparing the comments submitted on the FDA's proposed rule by ARUP Laboratories.

11. As described in greater detail below, I am deeply concerned about the FDA's final rule, the enormous costs it will impose on clinical laboratories, and the harm it will cause to patients across the nation. The FDA's final rule is based on a flawed understanding of how laboratories develop and provide professional testing services to help healthcare providers treat and diagnose patients. The rule poses serious risks to patients by threatening to reduce access to safe testing services over time, which will disproportionately harm patients with rare diseases, underserved patient populations, patients with cancer, and children.

ARUP Laboratories

12. ARUP Laboratories was founded 40 years ago in 1984 as an enterprise of the University of Utah's Department of Pathology. ARUP

Laboratories operates the hospital and outpatient clinical laboratories for one of the nation's most respected academic medical centers — University of Utah Health.

13. ARUP Laboratories is an academic, non-profit institution dedicated to providing hospitals and health systems with unparalleled quality testing services, particularly for otherwise unmet needs, while continuously adapting to the ever-changing needs of the healthcare industry.

14. ARUP Laboratories is a member of the American Clinical Laboratory Association ("ACLA"). Our Chief Executive Officer, Andy Theurer, is a member of the ACLA's Board of Directors.

15. ARUP Laboratories participates in the leading certification programs for clinical laboratories. It is accredited by the College of American Pathologists ("CAP-accredited") and certified by the International Organization for Standardization, which establishes the international standards for quality and competence in medical laboratory environments ("ISO 15189-certified"). It has also received certification by the Centers for Medicare and Medicaid Services under the requirements of the Clinical Laboratory Improvement Amendments of 1988 ("CLIA") ("CLIA-certified").

16. ARUP Laboratories is focused on providing hospitals and health care systems with unmatched professional clinical laboratory testing services, helping them to remain cost-effective and improve patient care. We believe in

collaborating, sharing knowledge, and contributing to laboratory science in ways that provide the best value for patients.

17. ARUP Laboratories is the nation's largest non-profit clinical reference laboratory. With more than 70 laboratory sections jointly located on its 700,000-square-foot main campus in Salt Lake City, Utah, ARUP Laboratories provides all types of comprehensive laboratory testing services, from routine screening tests to esoteric molecular and genetic assays. We provide professional services to more than 2,000 community hospitals and academic medical centers across the nation.

18. ARUP Laboratories has more than 4,000 employees, with a testing menu that offers hospitals and health centers access to more than 3,000 tests and test combinations. It processes an average of 70,000 specimens of blood, body fluid, and tissue per day, impacting more than 8 million patients each year.

19. ARUP Laboratories has more than 100 nationally and internationally recognized board-certified medical directors — including pathologists, subspecialty-qualified clinicians, and board-certified clinical scientists. Our MD and PhD certified professionals have extensive medical and scientific expertise to ensure that our testing services meet the ongoing clinical needs of health care providers and patients, while also providing clinical consulting services by telephone and secure email communications.

The expertise of our medical directors and scientists ensures an exceptionally high standard of quality, with each assay that ARUP Laboratories develops undergoing a rigorous and scientific validation process before it is added to the menu of testing services that ARUP Laboratories provides.

20. The ARUP Institute for Clinical and Experimental Pathology is the research and development arm of the organization, with over 60 scientists actively engaged in test development and optimization in collaboration with experts in the University's medical facilities. Over several decades, the Institute has developed, validated, verified, improved, and maintained at least 1,500 laboratory-developed tests.

21. Consistent with ARUP's academic foundations and its commitment to sharing knowledge with the clinical laboratory community, ARUP scientists and medical directors publish over 130 peer-reviewed articles each year. Collectively, we have published more than 3,400 scientific and clinical manuscripts in peer-reviewed journals to date.

22. In 2021, ARUP Laboratories completed a new, state-of-the-art 220,000-square-foot laboratory facility that spans four floors — the result of a substantial investment that ARUP Laboratories made, in reliance on the existing regulatory framework, to expand its ability to provide the highest quality services. The facility is designed to optimize quality laboratory testing, featuring world-class automation to provide efficient, large-scale laboratory

operations with the ability to reconfigure quickly. In addition to other improvements, the facility includes new space for ARUP's mass spectrometry laboratory, its automated core chemistry and immunology laboratories, and its specimen processing teams.

Professional Laboratory-Developed Testing Services

23. Professional laboratory-developed testing services are used by licensed practitioners in making health care decisions with their patients by providing diagnostic and other information that is used to monitor patients; influence medical, surgical, dietary, and other potential patient interventions; and inform future clinical advancements.

24. The testing services developed and performed by clinical laboratories have played a critical role in helping to diagnose and treat patients and are often at the forefront of innovation, particularly in academic and university clinical laboratory settings. For example, testing services that employ molecular diagnostics are routinely used in the diagnosis of malignancy, in the identification of genetic variants that suggest additional therapeutic interventions, in the characterization of genetic variants found in inheritable diseases, and in the diagnosis and treatment of infectious diseases. In many of these cases, no FDA-cleared or -approved medical devices are available, and physicians and patients rely on the professional testing services provided by laboratories to meet otherwise unmet needs, commonly when that

laboratory is not part of the same healthcare system in which the patient is receiving care.

25. Laboratory-developed tests are frequently developed in academic clinical laboratories and in reference (*e.g.*, referral) laboratories. For reference laboratories, requests for access to esoteric tests and services to diagnose rare disorders are relatively common, as specimens are received from clinics and hospital facilities extending over wider geographic areas or networks. Given the high costs of obtaining premarket approval or clearance from the FDA, as well as the limited financial incentives for medical device manufacturers to develop esoteric tests or tests for rare diseases, reference laboratories address unmet clinical needs by developing and offering professional testing services that are performed by clinical laboratory professionals in a single laboratory location.

26. As experts in clinical laboratory testing operations, clinical pathologists, doctoral-level clinical laboratory scientists, and laboratory personnel become aware of the strengths and limitations of different assays and testing platforms. This awareness comes from direct experience with assay and instrument operation, as well as peer-to-peer information sharing within the clinical laboratory community, scientific literature, and national and international conferences. When needed and appropriate, experts exercise

their professional judgment in seeking to modify, update, and validate testing procedures to address specialty care needs.

27. Test modifications are particularly important in clinical laboratory settings. For example, important issues include alternative specimen types (e.g., when the specimen type listed in an FDA-approved test is not the appropriate matrix for clinical evaluation), extension of specimen stability parameters, or automation of otherwise manual tests to improve throughput, quality, and efficiency of testing and to minimize risks of repetitive motion injuries to laboratory professionals. There are also times when modifying a test is necessary to adapt to specific patient needs or to adapt to urgent reagent shortages. Under CLIA's regulatory framework, the medical director of each laboratory is responsible for exercising professional judgment in deciding when to modify testing procedures to ensure that clinical testing is conducted appropriately, including validating the acceptability of the specimen used for testing. Under the FDA's final rule, many such modifications would require FDA premarket review, thus delaying and/or preventing service improvements to meet clinical and public health needs.

28. ARUP Laboratories provides a wide range of professional testing services to assist hospitals and health centers in deciding how best to diagnose and treat patients.

29. Genetic testing. ARUP's Institute for Clinical and Experimental Pathology was founded to foster the academic research of ARUP's medical directors, while also advancing the science of diagnostic laboratory medicine to improve patient care.

30. Under the leadership of its professional medical directors, ARUP Laboratories was one of the first laboratories to use DNA sequencing as part of the routine testing services provided to hospitals and health centers. ARUP Laboratories leveraged DNA sequencing technologies developed by Frederick Sanger that emerged in the 1980s and '90s and, more recently, ARUP has relied on next generation sequencing (known as massively parallel sequencing) technologies, which can be used to rapidly sequence whole genomes.

31. Building on these technological advances, many of ARUP's laboratory-developed genetic tests have resulted in successful innovations in the diagnosis and treatment of diseases.

32. One of ARUP's first genetic sequencing tests was a quantitative hepatitis C virus assay. Another notable test is ARUP's genetic panel for myeloid malignancy variants, which at the time it was developed in 2014, was one of the first tests available to detect and treat patients with diseases resulting from stem cell variants. In addition, ARUP Laboratories has developed rapid molecular tests for certain immunodeficiency disorders that use state of the art tools, such as next generation DNA sequencing, to find new

causes of primary immunodeficiencies, which can present from the newborn period until mid-to-late adulthood. ARUP Laboratories was also the first clinical reference laboratory to offer unique assays that measure the ability of a drug to inhibit tumor necrosis factor ("TNF") and detect the presence of antibodies that neutralize TNF antagonist drug activity which can lead to treatment failure.

33. Clinical toxicology. More than a decade ago, ARUP Laboratories introduced a new and innovative approach to panel-based drug testing that focused on improving efficiency and specificity of results, and at the same time, reducing costs. Instead of using exclusively immunoassays to screen specimens, ARUP Laboratories developed testing procedures that take advantage of the benefits of mass spectrometry. An immunoassay screen detects the presence of a targeted compound or similar compound by the signal that changes when the compound (or compounds) react with specifically formulated reagents. In contrast, mass spectrometry identifies each targeted compound that is present in a specimen individually based on mass-to-charge ratio, in combination with other unique chemical and physical characteristics. Tests that employ mass spectrometry can yield results with higher specificity than immunoassays, which translates to a lower risk of false-negative and false-positive results.

34. ARUP Laboratories is proud of the work that it does to support clients across the nation in cases of unknown drug exposures. For example, ARUP Laboratories developed a mass spectrometry test that targets detection of over 100 different compounds cited in data from the American Association of Poison Control Centers on the most common accidental exposures.

35. There are many ways clinical toxicology testing and therapeutic drug monitoring can be used to help patients. For example, laboratory-developed tests are often used to help cancer patients who are receiving different forms of chemotherapy. Similarly, laboratory testing is important when a patient receives a kidney transplant and is required to take immunosuppressant drugs to reduce the risk of rejecting the new organ. Therapeutic drug monitoring allows the physician to calibrate dosing correctly and help the patient avoid harmful side effects, such as infection. Laboratory-developed testing is also important when identifying and monitoring trace and toxic elements with industrial exposures.

36. Pharmacogenomics. ARUP Laboratories has made significant advances in the field of pharmacogenomics, an emerging medical specialty that employs genetic and phenotype testing to predict or explain patient response to certain medications. Laboratory-developed testing in this area can be used to guide selection of drug options and doses for individual patients while avoiding adverse drug effects.

37. As with many laboratory testing services, choosing the appropriate test and interpreting the results can be complicated and requires professional expertise. As a result, ARUP Laboratories often assists physicians in understanding the complexities associated with testing, including pharmacogenomics.

38. Maternal / pediatric health. Another area where ARUP Laboratories has advanced healthcare is in the areas of maternal and pediatric health. In parallel with the opioid epidemic, there has been a significant increase in newborns experiencing neonatal abstinence syndrome. The professionals at ARUP Laboratories spent years developing a new mass spectrometry test, using either meconium or umbilical cord tissue as the specimen type, that identifies almost 50 different types of compounds and can be used to assess in utero drug exposure.

39. ARUP Laboratories has collaborated with hospital delivery units as well as representatives from children and family services agencies across the nation to understand when new drugs should be added to its screening panels. For example, collaboration with clinicians and caregivers led ARUP to be among the first clinical laboratories to add gabapentin to its umbilical cord drug screening panel. That drug is often prescribed as an alternative to opioids or in combination with opioids for pain management but has been increasingly

recognized to precipitate and potentially worsen the severity of drug withdrawal symptoms in newborns.

40. ARUP Laboratories' expertise in newborn drug testing is having a positive impact on the development of public health programs. The close collaboration between ARUP's medical directors and professors at the University of Utah Department of Obstetrics and Gynecology has allowed researchers to identify the prevalence and trends in drug exposures. From a public health standpoint, this research has allowed more targeted interventions, including educating clinicians to talk with patients about substance use and pregnancy in affected regions and finding ways to link patients to multidisciplinary care and addiction services. Data collected has also been used in a successful grant application for resources to reduce morbidity and mortality from substance use disorders during pregnancy in Utah.

41. The Penelope Program. ARUP Laboratories is a key partner in the "Penelope Program" at University of Utah Health, which is a collaboration between ARUP Laboratories, the Department of Pediatrics, the Department of Human Genetics, the Utah Center for Genetic Discovery, the Center for Genomic Medicine, and the Primary Children's Hospital.

42. The program was launched in 2015 to address the challenge of undiagnosed diseases, recognizing that families often spend years — if not

decades — searching for answers to the unidentified illnesses affecting their children. The program brings together a team of experienced clinicians from multiple specialties, molecular geneticists, data scientists, and researchers who pool their knowledge and expertise to help evaluate pediatric patients from different angles and perspectives, to identify potential diagnoses, and to develop an appropriate diagnostic plan. The team has access to advanced technologies and diagnostic tools to look for diagnoses that may have been missed. New testing, such as whole genome sequencing and RNA sequencing, can unmask genetic causes hidden in the depths of a complex genome. The program is also actively engaged in reducing disparities in access to advanced diagnostics.

FDA's Final Rule Threatens Patient Health

43. The FDA's final rule improperly treats laboratory-developed tests as if they are manufactured medical devices. The rule reveals the FDA's fundamental misunderstanding of how laboratories perform professional testing services.

44. Laboratories are not manufacturers. And the tests they perform are not medical devices or other types of equipment. Instead, a laboratory-developed test is a professional service that reflects a series of procedures, medical protocols, and processes involved in analyzing tissue, blood, and other specimens as part of the practice of laboratory medicine. Those processes are

validated and overseen by experts who must exercise informed clinical judgment in assembling the technical steps involved in conducting a test, understand how those steps interact, and determine how data should be interpreted.

45. Mass spectrometers and other manufactured equipment used by healthcare professionals are only tools used in performing a laboratory-developed test. The test itself entails procedures, methodologies, and processes that do not qualify as instruments, apparatuses, machines, contrivances, implants, in vitro reagents, or other related articles subject to FDA regulation. When laboratory clinicians develop the processes and procedures necessary to perform laboratory-developed testing services, they are no different than other health care professionals who develop protocols or methodologies for treating patients or diagnosing diseases.

46. I am concerned that FDA's final rule takes the position that laboratory tests not cleared or approved by FDA are illegal and that laboratories have been violating the law for decades. Although the preamble to FDA's final rule says that the agency intends to exercise enforcement discretion — to allow laboratory-developed tests to remain on the market until it decides otherwise — the notion that laboratories and the professionals who run them are all engaged in unlawful conduct is absurd and, in my mind, shows

that the FDA itself is not acting reasonably and within the scope of any lawful authority granted by Congress.

47. I am also deeply concerned that, because the FDA lacks the resources to oversee tens of thousands of laboratory-developed tests, laboratories will face significant regulatory uncertainty and patients will face the risk of being denied access to the essential medical services they depend on clinical laboratories to provide. In short, the FDA's attempt to regulate laboratory testing services as medical device products will undermine the provision of health care and stifle innovation in a critical sector of our health care ecosystem.

48. FDA clearance and/or approval requirements will also have significant negative consequences for the innovation that occurs when professional laboratory clinicians modify existing testing procedures, or tailor them to address unmet patient needs.

49. Laboratory-developed tests can be modified to address a patient's specific circumstances, which can lead to the discovery of new and improved diagnostic approaches and testing protocols. This ability to innovate is likely to be curtailed under the FDA's new rule, which is likely to result in treating many of these modifications as creating a new "test" subject to separate FDA premarket review. This appears to also apply to minor modifications, such as adding manual immunoassays or PCR-based assays to simple liquid handlers,

for example. Through these requirements, quality improvements through automation are paradoxically disincentivized by the FDA.

50. Under the final rule, ARUP Laboratories and other clinical laboratories will have to devote significant resources to developing FDA-centric quality system processes and adhering to device submission requirements, including premarket submissions for modified and new laboratory-developed tests. But there are not enough laboratory professionals to support compliance with FDA's final rule while maintaining current testing levels.

51. Patient access to innovative tests will also be harmed because device regulation is likely to cause an FDA-review bottleneck going forward. That can only slow patient access to innovative tests as a result of extended review times, inadequate FDA resources to engage with applicants and developers, and clinically beneficial tests that are discontinued by laboratories due to excessive compliance costs over time.

52. FDA's final rule appears to recognize this concern by suggesting that it will not enforce certain requirements of federal law against laboratories that comply with New York requirements for laboratory testing. But that does not change the reality that tests not approved or cleared by FDA will be considered unlawful, and that FDA has made clear that it could change its enforcement guidelines at any time.

53. Even with the enforcement discretion announced in the final rule, the number of future premarket approval applications for laboratory-developed testing services will likely increase significantly. The FDA lacks the resources to deal effectively with these submissions, and, even if the FDA had more resources, there are not enough trained scientists and regulatory professionals for it to hire. The FDA will be competing with laboratories that also would need to increase hiring of the same professionals to deal with the new regulatory system.

54. The FDA's final rule also vastly overestimates the benefits of regulating professional testing services as the equivalent of medical devices. In suggesting that a large percentage of errors are attributable to laboratory tests, the FDA misapplies a study and reaches conclusions that are inconsistent with the diagnostic literature. A review of that literature suggests that only one to four percent of diagnostic errors may be attributable to faulty test results. As a result, and as explained in more detail in ARUP's public comment letter, it appears that in its initial regulatory impact analysis the "FDA has made, at a minimum, an approximately 250-fold overestimate in its assessment of financial benefit," failing to consider relevant data and applying only superficial assumptions. Unfortunately, it carries erroneous assumptions into calculations used in its final regulatory impact analysis, therefore still overestimating the purported financial benefits to society in the final rule. For

example, while the FDA cited our 2023 research manuscript [Rychert et al. Am J Clin Pathol. 2023. 160(3):297-302] in its final regulatory impact analysis when describing the percentage of clinician test orders that are laboratory-developed tests (3.9%), it more than doubled this percentage in its revised calculations of financial benefit, claiming that our data was based on "information for one single laboratory." This arbitrary increase in percentage, however, is in direct contradiction to the discussion of results in our manuscript, which states that "the presence of a national reference laboratory as part of the university health system may also have contributed to more LDTs being available for ordering than at other institutions. If this were the case, the present study's finding may *overrepresent* LDT orders vs those placed at other institutions." I therefore believe that the FDA has misapplied our study findings in its final regulatory impact analysis in a manner that overestimates the financial benefit to society.

55. The FDA's final rule understates the costs of treating professional laboratory services the same as medical devices. The rule is particularly problematic because it assumes — without sufficient or adequate analysis — that added FDA oversight would improve the safety and effectiveness of laboratory-developed tests, and yet it fails to take into account the reductions in access to safe testing that will occur if FDA's final rule remains in place.

56. The FDA's final rule will reduce access to safe testing because the staggering costs of seeking FDA approval threatens to force clinical laboratories over time to reduce the range of testing services they provide. In turn, that will disproportionally affect patients with rare diseases, underserved populations, patients with cancer, and children. For many laboratory-developed tests, market prices would increase due to reduced competition, and patients might lose timely access to diagnostic and treatment.

57. Hospitals and health centers trust the testing services provided by ARUP Laboratories because of our decades of experience in developing and performing tests, using them in our laboratories, and using them in consultation with expert clinicians for the care of their patients. Nearly all of our customer health systems are under different corporate ownership than ARUP Laboratories. Therefore, as written, the FDA's unmet needs exemptions in the final rule do not apply in our setting, and ongoing development of testing for unmet needs for the patients we serve will be more difficult under the final rule.

58. Under the FDA's final rule, new, and many modified existing, laboratory-developed tests would need to be submitted to the FDA for premarket review. But it is unrealistic to expect laboratories to be able to afford the massive costs involved in obtaining FDA clearance or approval of every test that they might develop in the future. Many laboratory-developed

tests are low-volume tests that are used infrequently. These are clinically essential tests for patients suffering from rare diseases or difficult-to-diagnose conditions, and they are often essential in developing effective treatment for patients who have unmet medical needs. But these types of tests often fail to generate sufficient revenues to justify going through the very expensive FDA-clearance or approval process, which is why testing is often performed in reference settings.

59. ARUP Laboratories is concerned about the negative impact of new regulatory requirements and premarket reviews on the clinical laboratory industry. ARUP Laboratories is also concerned that it may not be cost effective for many clinical laboratories to continue to develop new, low-volume tests that can be used to diagnose or monitor rare diseases, particularly given the restrictions on testing for unmet needs in patients seen in facilities outside a laboratory's corporate ownership.

60. Diverting resources away from helping patients and toward seeking FDA clearance or approval of testing services that FDA lacks the resources and expertise to evaluate would not benefit patients or the public interest. Indeed, the most alarming consequence of FDA's rule is to declare all existing laboratory-developed tests to be unlawful and to make it more difficult for patients to continue to obtain the essential testing services they need.

In accordance with 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on this 23 day of May, 2024.

By: Jonathan Genzen MD, PhD
Jonathan Genzen, M.D., Ph.D.