UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
SHERMAN DIVISION

AMERICAN CLINICAL LABORATORY ASSOCIATION, et al., Plaintiffs, v. U.S. FOOD AND DRUG ADMINISTRATION, et al., Defendants.	Civil No.: 4:24-CV-479-SDJ
ASSOCIATION FOR MOLECULAR PATHOLOGY, et al., Plaintiffs, v. U.S. FOOD AND DRUG ADMINISTRATION, et al., Defendants.	Civil No.: 4:24-CV-824-SDJ

MEMORANDUM OF AMICI CURIAE PUBLIC CITIZEN, AMERICAN CANCER SOCIETY CANCER ACTION NETWORK, ASSOCIATION FOR CLINICAL ONCOLOGY, FRIENDS OF CANCER RESEARCH, NATIONAL BRAIN TUMOR SOCIETY, AND OVARIAN CANCER RESEARCH ALLIANCE IN SUPPORT OF DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT AND IN OPPOSTION TO PLAINTIFFS' MOTIONS FOR SUMMARY JUDGMENT

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INTEREST OF AMICI CURIAE

As detailed in the motion to file submitted concurrently herewith, amici curiae Public Citizen, American Cancer Society Cancer Action Network (ACS CAN), Association for Clinical Oncology (ASCO), Friends of Cancer Research, National Brain Tumor Society, and Ovarian Cancer Research Alliance are nonprofit advocacy organizations with a shared interest in public health, including medical device safety and effectiveness. Amici support the decision of the Food and Drug Administration (FDA) to regulate laboratory developed tests as medical devices under the Food, Drug, and Cosmetic Act (FDCA). Amici believe that FDA regulation is necessary to ensure the safety and effectiveness of laboratory developed tests and are concerned that plaintiffs' challenge, if successful, would result in substantial harm to patients who rely on such tests to diagnose and treat cancer and other medical conditions.

INTRODUCTION

This action challenges an FDA final rule concerning regulation of laboratory developed tests under the medical device provisions of the FDCA. *See* 89 Fed. Reg. 37286 (2024) (Final Rule). The FDCA authorizes the FDA to regulate medical devices and defines "device" based on the functions that it performs—not on the type of the entity that manufactures it. Applying the statutory definition, FDA regulations have long treated in vitro diagnostic products as medical devices. Exercising its enforcement discretion, however, the FDA declined to regulate certain of those products, so-called "laboratory developed tests," although the tests satisfied the statutory definition of device and the regulatory definition of in vitro diagnostic products.

Whether the FDA's exercise of enforcement discretion was ever wise, the FDA has now recognized that its basis for regulating laboratory developed tests differently from similar devices made by other types of manufacturers is outdated. Accordingly, in the final rule at issue here, the FDA, without altering the substance of its definition of "in vitro diagnostic products," clarified that a device that satisfies the definition is subject to regulation under the FDCA "including when the manufacturer of these products is a laboratory." 89 Fed. Reg. at 37445 (amending 21 C.F.R. § 809.3).

The FDA rule is consistent with the statutory text—indeed, compelled by it—and is justified by the increasing use and complexity of laboratory developed tests. Contrary to plaintiffs' contention, the Clinical Laboratories Improvement Act (CLIA) is no substitute for FDA regulation of medical devices manufactured by laboratories. CLIA does not displace the FDCA but complements it, and full implementation of *both* statutes is vital to assuring that Congress's framework for protecting patients who rely on medical testing is fully realized. This Court should uphold the FDA's action.

ARGUMENT

I. THE FDA'S DECISION TO REGULATE LABORATORY DEVELOPED TESTS IS WELL-SUPPORTED BY THE FDCA.

A. The statutory definition of medical devices looks to function, not the identity of the manufacturer.

1. In 1976, Congress enacted the Medical Device Amendments of 1976 (MDA), Pub. L. No. 94-295, 90 Stat. 539, to amend the FDCA to grant federal regulators "significant new authority … to assure the safety and effectiveness of medical devices intended for human use." H.R. Rep. No. 94-853, at 3 (1976). The FDCA defines

"device" to mean "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory … intended for use in the diagnosis of disease or other condition, or in the cure, mitigation, treatment, or prevention of disease," other than drugs and certain software. 21 U.S.C. § 321(h)(1). That definition, and whether an item is a medical device, looks to the intended function of the item, not to its manufacturer.

Under the MDA, the FDA applies varying levels of regulation to a medical device based on the risk to safety and effectiveness presented by the device. *See* 21 U.S.C. § 360c(a). All device manufacturers must register with the FDA, must label their devices to instruct the user on proper use, must comply with current good manufacturing practices, are accountable for marketing adulterated or misbranded devices, and must submit reports of adverse events associated with their devices to the FDA, among other things. 21 U.S.C. §§ 351, 352, 360, 360i; 21 C.F.R. §§ 807.20, 809.10, 820.1 *et seq*. In addition, devices that present a higher risk to safety and effectiveness must undergo premarket approval, which requires the manufacturer to submit "valid scientific evidence" that provides a reasonable assurance that the device is safe and effective. 21 U.S.C. §§ 360c(a), 360e; *see* 21 C.F.R. § 860.7.

2. Applying the statutory definition of "device," the FDA has long regulated "in vitro diagnostic products" as medical devices. *See* 45 Fed. Reg. 7474, 7484 (1980); *see also* 41 Fed. Reg. 6896, 6903 (1976). FDA regulations define in vitro diagnostic products as "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order

to cure, mitigate, treat, or prevent disease or its sequelae" and that "are intended for use in the collection, preparation, and examination of specimens taken from the human body." 21 C.F.R. § 809.3(a). This longstanding regulatory definition easily encompasses laboratory developed tests that perform those functions. "[M]any test systems made by laboratories today are functionally the same as those made by other manufacturers," including being made by "the same materials and technologies," having "the same or similar purposes," being "developed by and for individuals with similar expertise," and being "marketed to the same patients, sometimes on a national scale." Proposed Rule, 88 Fed. Reg. 68006, 68009–10 (2023).

The FDA historically exercised enforcement discretion with respect to laboratory developed in vitro diagnostic tests, choosing not to "enforce[] requirements related to registration and listing, reporting adverse events to FDA, current good manufacturing practices …, or premarket review … prior to use of the [test] in patient care, among other requirements." Final Rule, 89 Fed. Reg. at 37289. The agency's earlier exercise of discretion not to enforce its regulatory authority does not alter the provisions of the FDCA. And under the plain language of the FDCA, laboratory developed diagnostic tests, like other diagnostic tests, fit comfortably within the definition of devices.

B. The rulemaking record demonstrates the need for FDA to regulate laboratory developed tests as medical devices, just as they have long regulated other diagnostic tests.

The FDA's decision to conform its enforcement policy to the FDCA's definition of "device" and the regulatory definition of "in vitro diagnostic products" has ample support in the administrative record. The record confirms that laboratory developed

tests today play an increasingly critical role in the diagnosis and treatment of disease and that FDA regulation is needed to ensure that devices manufactured by laboratories are safe and effective, just as devices manufactured by other types of entities must be.

1. "Diagnostic testing is a cornerstone of modern medicine." Proposed Rule, 88 Fed. Reg. at 68010. According to the Division of Laboratory Systems of the Centers for Disease Control and Prevention (CDC), "14 billion laboratory tests are ordered annually," and "70% of today's medical decisions depend on laboratory test results" performed by the 260,000 laboratories certified under CLIA.[1] Today, such tests are "ubiquitous," and are intended "for use in complex areas of medicine involving life-threatening diseases," including "neurological diseases, cardiovascular illness, infectious diseases, and rare diseases." Proposed Rule, 88 Fed. Reg. at 68010.

Laboratory developed tests are particularly "critical in the management of cancer,"[2] and are "increasingly being used to guide therapeutic decisions for people with cancer."[3] Advances in DNA analysis "have facilitated hereditary cancer risk prediction and improved molecular diagnosis, resulting in a panoply of tests for

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[1] CDC, Division of Laboratory Systems, https://www.cdc.gov/csels/dls/strengthening-clinical-labs.html (CDC Labs Webpage).

[2] Comments of ACS CAN, Docket No. FDA-2023-N-2177 (Dec. 4, 2023), at 1 (ACS CAN Comments), https://www.regulations.gov/comment/FDA-2023-N-2177-6396.

[3] Comments of ASCO, Docket No. FDA-2023-N-2177 (Dec. 4, 2023), at 3 (ASCO Comments), https://www.regulations.gov/comment/FDA-2023-N-2177-6650.

inherited disease risk and presymptomatic disease detection."[4] And medical advances have made cancer care "more complex and increasingly personalized," making it "more important than ever to ensure that new diagnostic tests are of the highest quality."[5] The importance of safe and effective laboratory tests, however, is not confined to cancer diagnosis and treatment. They are also used to screen for medical issues during pregnancies and were widely used to test for infection during the COVID-19 pandemic.[6] Indeed, in all medical situations, providing appropriate care to the patient "requires quality diagnostics."[7]

The medical community's current reliance on laboratory tests is a seismic shift from where things stood when the MDA was enacted in 1976. At that time, most laboratory developed tests "served a limited number of patients—typically those living near the labs that developed them." Pew Report 1–2. Today, such tests are "often used in laboratories outside of the patient's healthcare setting and are often manufactured in high volume for large and diverse populations." Proposed Rule, 88

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[4] Kenneth Offit, et al., *Regulation of Laboratory-Developed Tests in Preventive Oncology: Emerging Needs and Opportunities*, 41 J. Clinical Oncology 11, 11 (2023) (Offit Study), https://ascopubs.org/doi/10.1200/JCO.22.00995#tbl1 (footnote omitted).

[5] ASCO Comments 2 (emphasis omitted).

[6] *See* The Pew Charitable Trusts, *The Role of Lab-Developed Tests in the In Vitro Diagnostics Market* 1 (Oct. 22, 2021) (Pew Report), https://www.pewtrusts.org/-/media/assets/2021/10/understanding-the-role-of-lab-developed-tests-in-vitro-diagnostics.pdf; *see also* Sarah Kliff & Aatish Bhatia, *When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong*, N.Y. Times, Jan. 1, 2022, https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html; Proposed Rule, 88 Fed. Reg. at 68010.

[7] Comments of Patient Advocacy Organizations, Docket No. FDA-2023-N-2177 (Nov. 30, 2023), at 1, https://www.regulations.gov/comment/FDA-2023-N-2177-5914.

Fed. Reg. at 68009. They "can reach millions of people," including through direct shipment to consumers' homes "without a doctor's prescription." Pew Report at 2.

Devices offered as laboratory developed tests are thus "a growing share of the testing market." Proposed Rule, 88 Fed. Reg. at 68010. One report projects that the international market for laboratory developed tests will grow at an annual rate over 7 percent between 2024 and 2030, with the U.S. market experiencing the "fastest" growth over that period.[8] "Many [laboratory developed tests] are manufactured by laboratory corporations that market [tests] nationwide, as they accept specimens from patients across the country and run their [tests] in very large volumes in a single laboratory." Final Rule, 89 Fed. Reg. at 37289. And with laboratories "taking in large numbers of testing samples from around the country," "the impact of even one inaccurate test can [affect] thousands of lives."[9]

In addition to their ubiquity, laboratories today "run far more complex and high-risk tests for a wider range of uses than in 1976." Pew Report 1. These uses include "choosing a cancer treatment," "managing a pregnancy," and "fight[ing] against COVID-19." *Id.* (footnote omitted). With respect to cancer tests in particular, the "FDA has witnessed an explosion in the volume, complexity, and scope of [devices offered as laboratory developed tests] for use in determining cancer treatments." Proposed Rule, 88 Fed. Reg. at 68010.

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[8] Grand View Research, Laboratory Developed Tests Market Trends, https://www.grandviewresearch.com/industry-analysis/laboratory-developed-tests-market-report.

[9] Comments of U.S. PIRG, Docket No. FDA-2023-N-2177 (Dec. 1, 2023), at 2 (PIRG Comments), https://www.regulations.gov/comment/FDA-2023-N-2177-6468.

Given these developments, the FDA was on solid ground in concluding that the "risks associated with most [laboratory developed tests] today are … much greater than they were at the time FDA began implementing the MDA, and most [such tests] today are similar to other [in vitro diagnostic products] that have not been under FDA's general enforcement discretion approach." Final Rule, 89 Fed. Reg. at 37289.

2. In light of the medical profession's increasing reliance on the information produced by ever more sophisticated laboratory developed tests, the FDA's hands-off policy no longer fulfilled the FDCA's goal of ensuring that medical devices are safe and effective. *See* 21 U.S.C. §§ 360c–360e. Laboratory developed tests "are relied upon for high stakes medical decisions," and the "consequences of false results in these contexts can include spread of disease, missed diagnoses, misdiagnoses, use of ineffective treatments with toxic side effects, and lack of use of life-saving treatments." Final Rule, 89 Fed. Reg. at 37312. Indeed, the CDC estimates that between 40,000 to 80,000 "deaths occur annually from preventable diagnostic errors." CDC Labs Webpage, *supra*, note 1.

Tests that are not safe and effective harm patients by producing false positive or false negative results.[10] False positive results "erroneously indicate that a patient has a certain disease or condition." Proposed Rule, 88 Fed. Reg. at 68010. A false

[10] Comments of Center for Science in the Public Interest, Docket No. FDA-2023-N-2177 (Dec. 4, 2023), at 1 (CSPI Comments), https://www.regulations.gov/comment/FDA-2023-N-2177-6641 ("Reliable [tests] are crucial, as inaccurate tests can lead, on the one hand, to failure to diagnose critical diseases or conditions (false negatives) and, on the other, to inappropriate treatment for diseases or conditions patients do not have (false positives)."); *see also* PIRG Comments 2.

positive outcome can be brutal for affected patients, "leading to expensive, stressful, and potentially dangerous overtreatment," CSPI Comments 3, and delay in "diagnosis and treatment of the true disease or condition," Proposed Rule, 88 Fed. Reg. at 68010. A false negative result "can lead to progression of disease, in some cases without the opportunity for life-saving treatment, and the spread of infectious disease." *Id.*

False test results cause economic harm as well. For instance, the FDA described "a false positive result from a genetic test for long QT syndrome (a heart signaling disorder) that led to the erroneous implantation of a defibrillator in a healthy individual." Proposed Rule, 88 Fed. Reg. at 68010; *see also id.* at 68010–12 (detailing reported problems with laboratory developed tests). And the FDA cited a 2015 study that found that false-positive Lyme disease tests "resulted in $1,226 in unnecessary treatment costs" for each affected patient and "every false-positive ovarian cancer test led to $12,578 in such costs," while "every false-negative result for breast cancer cost $775,278 in lifespan lost (about three life-years)."[11]

The FDA noted recently published studies "document[ing] high variability in performance among" devices offered as laboratory developed tests. Proposed Rule, 88 Fed. Reg. at 68010. For instance, in one study, only 7 of 19 laboratories using their own manufactured tests "correctly reported all results," and "[f]or almost half of the tests studied, analytical accuracy was significantly lower than that of the parallel test

[11] CSPI Comments 3 (referencing FDA, *The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies* 8–14 (Nov. 16, 2015) (2015 Report), https://www.regulations.gov/document/FDA-2023-N-2177-6969).

approved by FDA."[12] Another study of early detection cancer tests identified a test that "delivered nine false positive results for every true cancer diagnosis." Proposed Rule, 88 Fed. Reg. at 68011 (citing Offit Study). And the FDA documented its own experience with laboratory developed tests, providing examples of tests "with reported or known issues" of which the agency was aware.[13] For example, the FDA received reports of false positive and false negative results from tests used across seven laboratories for non-invasive prenatal screening, as well as reports of problems with multiple tests used to detect cancer. Schuck Memo 3–5. These reports have steadily increased in recent years, from "four concerns" identified between 2008 and 2011 to "23 concerns between 2020 and 2023." Final Rule, 89 Fed. Reg. at 37322 n.52.

The New York Department of Health's Clinical Laboratory Evaluation Program (CLEP) also offered its experience in regulating laboratory developed tests.[14] CLEP noted that more than half of such tests submitted to it could not be

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[12] Proposed Rule, 88 Fed. Reg. at 68011 (citing J.D. Pfeifer *et al.*, *Reference Samples To Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics*, 157 Am. J. Clinical Pathology 628 (Apr. 2022), https://doi.org/10.1093/ajcp/aqab164); *see also* Final Rule, 89 Fed. Reg. at 37293 ("[E]ven under the reanalysis, the laboratory tests had worse performance, with only 8 of 19 laboratories correctly reporting all variants (compared to 7 in the original analysis).").

[13] Final Rule, 89 Fed. Reg. at 37321 (citing Memo. to File from Brittany Schuck, Ph.D., Deputy Off. Dir., Off. of In Vitro Diagnostics (OHT7), Ctr. for Devices and Radiological Health (CDRH), FDA, RE: Examples of In Vitro Diagnostic Products (IVDs) Offered as Laboratory Developed Tests (LDTs) that Raise Public Health Concerns (Sept. 22, 2023) (Schuck Memo), https://www.regulations.gov/document/FDA-2023-N-2177-6866).

[14] Comments of CLEP, FDA-2023-N-2177 (Nov. 22, 2023), at 1, https://www.regulations.gov/comment/FDA-2023-N-2177-4963.

approved based on the original application, and "approximately 10% of these tests (2% of approved tests) required four or more rounds of review." *Id.* at 2. Reasons for non-approval include "design flaws, inadequate validation data, and process problems that call into … question the reliability of results." *Id.*

3. In light of the foregoing and other record evidence, the FDA had ample justification to end its enforcement discretion and regulate laboratory developed tests as "devices" under the FDCA. As the agency explained, the tools of the FDCA—"adverse-event reporting, establishment registration and product listing, labeling standards, investigational controls, [current good manufacturing practices], and premarket review"—"effectively serve the public" by helping to "ensure product safety and effectiveness." Final Rule, 89 Fed. Reg. at 37291. For example, through medical device reporting requirements, the FDA can "aggregate[]" information about devices to enable it to detect "issues that a single laboratory may never see." *Id.* The FDA "has identified and helped resolve a wide range of [in vitro diagnostic device] issues using this type of information." *Id.* As one example, the FDA described how high dose biotin supplements had caused "inaccurate results" in tests called immunoassays. *Id.* Adverse event reporting helped the FDA identify the problem, which led many manufacturers to redesign their tests. *Id.* In this way, required reporting enabled the FDA to "catch[] and address[] potentially problematic [devices] to better protect the public." *Id.*

The registration and listing requirements of the FDCA "also have substantial public health value." *Id.* The information furnished to the FDA provides the agency

"with the location of device establishments and all devices manufactured at those establishments," which "allows for effective planning, coordinating, and scheduling of inspections." *Id.* Inspections, in turn, can apprise the FDA of "design changes that fundamentally alter the [device's] safety or effectiveness and present novel risks to patients," "give [the] FDA better information about the universe of [devices] on the market," and allow the FDA to "protect the public through more comprehensive remediation efforts." *Id.* Registration and listing also provides patients and physicians a "better understand[ing] of the different testing options that are available and the source and location of those testing options" because, absent the FDA's new rule, "there is no reliable inventory of [devices] on the market." *Id.* Indeed, because the FDA in the past declined to enforce the FDCA as to these diagnostic products, it does not even "know exactly how many [devices] are currently offered as [laboratory developed tests], precisely what those [devices] are used for, or the exact breadth of the reach of those [devices]." *Id.* at 37313. The FDCA's registration and listing requirements will provide the FDA with this critical information.

II. CLIA DOES NOT ALTER THE FDCA'S REQUIREMENTS OR OBVIATE THE IMPORTANCE OF REGULATING LABORATORY DEVELOPED TESTS AS MEDICAL DEVICES.

Although the benefits of FDA regulation of laboratory developed tests are incontrovertible, plaintiffs argue that the FDA should have stayed its hand because laboratories are subject to regulation under CLIA. In so arguing, however, plaintiffs do not identify anything in the statutory text of either CLIA or the FDCA indicating that Congress intended the former to displace the latter—and for good reason: CLIA

regulation complements, and is not a substitute for, the FDCA regulation of medical devices.

1. Whereas the FDCA provides the FDA with the tools needed to regulate medical *devices*—for example, by requiring registration, listing, and medical device reporting—CLIA focuses on laboratory *procedures*. For instance, CLIA prohibits soliciting or accepting "materials derived from the human body for laboratory examination or other procedure" unless the Centers for Medicare and Medicaid Services (CMS), which implements CLIA, has issued a certificate "applicable to the category of examinations or procedures which includes such examination or procedure." 42 U.S.C. § 263a(b). To obtain a certificate, a laboratory must provide CMS with a description of "the characteristics of the laboratory examinations and other procedures performed by the laboratory," including the number, types, and methodologies of examinations and procedures and "the qualifications (educational background, training, and experience) of the personnel directing and supervising the laboratory and performing the laboratory examinations and other procedures." *Id.* § 263a(d). CLIA also authorizes CMS to "issue standards to assure consistent performance by laboratories … of valid and reliable laboratory examinations and other procedures," *id.* § 263a(f)(1), and requires a laboratory to undergo proficiency testing for "each examination and procedure conducted within a category of examinations or procedures for which it has received a certificate," *id.* § 263a(f)(3)(A). The statute's repeated references to laboratory "examinations" and "procedures"

reflect that CLIA is concerned with "laboratory practices and the protocols and standards in those laboratories," not with medical devices themselves.[15]

Several provisions of the FDCA highlight this distinction. With respect to medical devices that the FDA authorizes for emergency use, for instance, the FDCA authorizes the FDA to "determine that a laboratory examination or procedure associated with such device shall be deemed, for purposes of [CLIA], to be in a particular category of examinations and procedures." 21 U.S.C. § 360bbb-3(m)(1). This provision draws a clear distinction between a "device," which falls under the ambit of the FDCA, and a "laboratory examination or procedure associated with such device," which falls under CLIA's ambit.[16]

To be sure, CMS regulations do not wholly ignore the devices used by laboratories to perform testing. For instance, CMS regulations require laboratories to assure that test systems satisfy "performance specifications," with in-house systems being subject to "performance characteristics" beyond those required for

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[15] *Examining the Regulation of Diagnostic Tests and Laboratory Operations Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 114th Cong. 36 (2015) (2015 Hearing) (statement of Patrick Conway, M.D., Acting Principal Deputy Administrator, Deputy Administrator for Innovation and Quality, and Chief Medical Officer, CMS, Dep't of Health and Human Services).

[16] See *FDA and CMS Statement: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made* (Jan. 17, 2024) (FDA-CMS Joint Statement) ("The FDA and CMS both provide oversight to help assure the accuracy of test results, however, they have different roles."), https://www.cms.gov/newsroom/press-releases/fda-and-cms-statement-americans-deserve-accurate-and-reliable-diagnostic-tests-wherever-they-are; Final Rule, 89 Fed. Reg. at 37291 (explaining that CLIA focuses on "individual laboratory operations," while the FDCA "is focused on identifying problems" with devices, "such as design or other manufacturing problems").

laboratories using FDA-approved test systems. 42 C.F.R. § 493.1253. As CMS has explained, these requirements are designed to ensure that a laboratory developed test has "analytical validity," that is, that "a specific test finds what it is supposed to find (i.e. the analyte it is intended to detect) when laboratories perform testing on patient specimens."[17]

CLIA, however, "does not regulate critical aspects of laboratory test development," such as a regulatory evaluation of "the performance of a test before it is offered to patients and health care providers" and "design controls." Final Rule, 89 Fed. Reg. at 37313; *see also* FDA-CMS Joint Statement ("CMS does not have the expertise to assure that tests work; the FDA does."). In particular, CLIA "does not assess clinical validity (i.e., the accuracy with which a test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient)." Final Rule, 89 Fed. Reg. at 37313; *see also* 2015 Hearing 60 (testimony of Dr. Conway of CMS that CMS does "not do assessments of clinical validity, meaning the test actually identifies the condition, the absence or presence of the condition that it is supposed to identify.").

By way of illustration, in 2008, researchers claimed that a test for detecting ovarian cancer could predict who had the disease 99.3 percent of the time. *See* 2015 Report 11. That test worked by "measuring the levels of 6 proteins in a blood

[17] CMS, CLIA Overview (Oct. 22, 2013) (CLIA FAQs), https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ldt-and-clia_faqs.pdf; *see also* 2015 Hearing 60 ("On the CMS perspective, we do basic assessment of analytical validity so the analyte is the actual analyte in the test." (testimony of Dr. Conway of CMS)).

sample."[18] But "[w]ith only CLIA oversight, [the laboratory] was not required to prove that the 6 proteins the test detected could accurately predict disease," and the test "was rushed to market before this crucial validation step and was later found to have an unfortunately high false positive rate." *Id.* Thus, the test may have had analytical validity, *i.e.*, it may have detected the proteins it was designed to detect, but it lacked clinical validity because it returned many false positives regarding the presence of ovarian cancer. 2015 Report 11. And without clinical validity, which is something CLIA regulation does not address, a device lacks "sufficient assurances of safety and effectiveness" to pass muster under the FDCA's standards. Final Rule, 89 Fed. Reg. at 37313.

In short, notwithstanding the common objective of protecting patients who depend on safe and effective medical diagnosis and treatment, CLIA and the FDCA employ different regulatory tools to tackle different problems, tailored to their respective spheres.

2. Plaintiffs "carry[] a 'heavy burden'" in arguing that "one statute 'displaces' a second." *Dep't of Agric. Rural Dev. Rural Housing Serv. v. Kirtz*, 601 U.S. 42, 64 (2024) (quoting *Epic Sys. Corp. v. Lewis*, 584 U.S. 497, 510 (2018)). Even when two statutes touch "on the same topic," there is a "'strong presumption' they can coexist harmoniously." *Id.* (quoting *Epic Sys. Corp.*, 584 U.S. at 510). "Where two laws are

[18] Rep. Louise M. Slaughter, MPH, *FDA Oversight of Laboratory Developed Tests Essential for Patient Health and Safety*, 20 Am. J. Managed Care (Sept. 2014), https://www.ajmc.com/view/fda-oversight-of-laboratory-developed-tests-essential-for-patient-health-and-safety.

merely complementary," a court's "duty lies not in preferring one over another but in giving effect to both." *Id.*

Here, the Court should reject plaintiffs' argument that CLIA displaces the FDCA. No provision of either statute contains "a clearly expressed congressional intention that such a result should follow." *Epic Sys. Corp.*, 584 U.S. at 510 (internal quotation marks omitted). Rather, to the extent that CLIA and the FDCA cross-reference each other, they do so in a way that highlights their complementary nature. CLIA, for instance, authorizes CMS to issue a "certificate of waiver" from certain CLIA requirements to a laboratory that "only performs examinations and procedures" that "have been approved" by the FDA "for home use." 42 U.S.C. § 263a(d)(2), (3) . In other words, Congress provided that a laboratory that processes tests involving only FDA-approved devices can be exempt from some (but not all) of CLIA's requirements. *See* 42 C.F.R. §§ 493.15(c), (e); 493.35–.37. Similarly, as described above, when the FDA authorizes a device for emergency use, it may provide that the device "shall be deemed, for purposes of [CLIA], to be in a particular category of examinations and procedures." 21 U.S.C. § 360bbb-3(m)(1).

Thus, in CLIA and the FDCA, Congress recognized the existence of the other statute and enacted specific provisions to address areas of potential overlap, without ever suggesting that CLIA wholly displaces application of the FDCA to medical devices manufactured by laboratories. "[T]he idea that one of these two complementary [statutes] must 'prevail' over the other is mistaken." *Gallardo v. Marstiller*, 596 U.S. 420, 432 (2022); *see Epic Sys. Corp.*, 584 U.S. at 510 (holding that

Congress's "intention" to displace a statute "must be 'clear and manifest'" (quoting *Morton v. Mancari*, 417 U.S. 535, 551 (1974)).

3. CMS itself has long recognized CLIA's limitations and the importance of the FDA's complementary role. As CMS has explained, although CLIA regulation requires laboratories to satisfy "certain performance characteristics relating to analytical validity," that requirement is "limited … to the conditions, staff, equipment, and patient population of the particular laboratory" and "are not meaningful" in other contexts. CLIA FAQs 1. Moreover, analytical validity is reviewed during a biennial survey, "after the laboratory has already started testing." *Id.* Meanwhile, "the FDA's premarket clearance and approval processes assess the analytical validity of a test system in greater depth and scope," and "also assess clinical validity," which CLIA does not address. *Id.* Thus, CMS recognizes that "the two agencies' regulatory schemes are different in focus, scope and purpose, but they are intended to be complementary." *Id.*

Indeed, the FDA has never been walled off from regulation of laboratory activities. Even before passage of CLIA in 1988, the FDA played a role in the oversight of the devices and other technical aspects of lab testing.[19] No provision in CLIA removes the FDA's pre-existing authority under the FDCA over medical devices manufactured by laboratories.

[19] *Clinical Laboratory Improvement Act Before the Subcomm. on Health and the Environment of the H. Comm. on Energy and Commerce*, 100th Cong. 77 (1988) (testimony of Dr. William L. Roper).

Far from being mutually exclusive statutory regimes, CLIA and the FDCA are complementary statutes, each playing a distinct role in assuring that patients and physicians can rely on medical devices (regardless of their manufacturer) used to diagnose, treat, and manage disease and the laboratories that perform testing (regardless of whether they also manufacture devices). CMS does not and cannot fill the FDA's role in this area. Not only does CMS lack the authority to do premarket review, to require compliance with good manufacturing practices, and to require reporting of adverse events, among other things, CMS also "does not have scientific staff capable of reviewing complex medical and scientific literature in determining clinical validity. This expertise resides within the FDA." 2015 Hearing 25 (testimony of Dr. Conway of CMS); *see id.* at 38 (stating that CMS staff "are not trained to assess premarket scientific literature and determine clinical validity").

Thus, interpreting the term "device" in the FDCA to exclude laboratory developed tests, as the plaintiffs here urge, would undermine the framework that Congress created for assuring patient safety. The Court should reject that reading and uphold the FDA's rule as the best interpretation of the plain language of the statutory definition.

CONCLUSION

For the foregoing reasons, the Court should grant defendants' motion for summary judgment and deny plaintiffs' cross-motion for summary judgment.

November 4, 2024

Respectfully submitted,

/s/ *Nandan M. Joshi*

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CERTIFICATE OF SERVICE

I hereby certify that on this date, the foregoing document was electronically filed in this matter with the Clerk of Court, using the ECF system, which sent notification of such filing to all counsel of record.

/s/ *Nandan M. Joshi*

November 4, 2024