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.	Case No.: 4:24-cv-479 **COMPLAINT**

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COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiffs American Clinical Laboratory Association ("ACLA") and HealthTrackRX Indiana, Inc. and HealthTrackRX, Inc. (together "HealthTrackRX") bring this action against the Food & Drug Administration ("FDA"), the Department of Health and Human Services, and the Secretary of Health and Human Services and the FDA Commissioner in their official capacities, challenging the final rule published on May 6, 2024, announcing FDA's intent to regulate laboratory-developed tests as medical devices under the Federal, Food, Drug and Cosmetic Act. Because the final rule exceeds FDA's lawful authority and is arbitrary and capricious and contrary to law, the rule should be set aside and vacated, and defendants should be enjoined from enforcing or implementing the rule. *See* 5 U.S.C. § 706. Plaintiffs allege as follows:

PRELIMINARY STATEMENT

1. The professional diagnostic testing services provided by clinical laboratories are an essential part of the nation's healthcare system. These important testing services have long been relied on by healthcare providers to diagnose and develop appropriate treatments for patients who suffer from illness and disease. There are thousands of laboratories across the United States that offer tens of thousands of molecular and other types of high-quality diagnostic testing services to providers and patients. These testing services are

a critical pillar of our nation's health care system.

2. For decades, laboratory-developed testing services (often referred to as "LDTs") have been regulated under a statutory and regulatory framework—the Clinical Laboratory Improvement Amendments Act of 1988 ("CLIA")—that imposes numerous laboratory-specific standards to ensure the validity and reliability of laboratory diagnostic testing services, including the training and qualifications of the skilled professionals who perform, supervise, and interpret those tests. When creating and performing testing services, these laboratory professionals have not generally been required to comply also with the costly and burdensome pre-approval and clearance requirements that the Federal Food, Drug and Cosmetic Act ("FDCA") authorizes FDA to apply to manufactured medical devices sold in interstate commerce. Nor has Congress ever granted FDA authority to regulate professional laboratory-developed testing services.

3. FDA's final rule threatens to upend the nation's entire laboratory profession by seeking to regulate all laboratory-developed tests as if they are medical devices under the FDCA. In asserting authority to transform the regulatory framework that has applied for decades, FDA cannot point to any new statutory authority granted by Congress. Nor can FDA contend that Congress has ever provided it with the resources that would be necessary to retain the personnel and build the expertise necessary to exercise sweeping

authority over the thousands of testing services provided by the nation's laboratories. To the contrary, Congress has recently entertained legislative proposals that would have granted FDA new authority to regulate laboratory-developed testing services, and it has declined to provide FDA that power.

4. FDA's final rule relies on the extraordinary position that in 1976, when Congress expanded FDA's authority to regulate medical devices, it also quietly intended to outlaw—and subject to substantial civil and criminal monetary penalties—any professional laboratory-developed testing services that were not first approved or cleared by FDA. The logic of FDA's position is that tens of thousands of professionals across the country performing millions of diagnostic testing services every year, working with thousands of doctors and patients, have for decades done so in open and direct violation of the law. According to FDA, the only reason laboratories have not been civilly and criminally punished is because FDA has chosen to exercise unreviewable "enforcement discretion." In short, FDA is taking the position that a "long-extant statute" grants it vast, "transformative" regulatory powers that it has not previously exercised—a position that courts have rightly approached with deep skepticism. *West Virginia v. EPA*, 597 U.S. 697, 724 (2022) (quoting *Util. Air Regul. Grp. v. EPA*, 573 U.S. 302, 324 (2014)).

5. If it is not vacated, FDA's unprecedented final rule will have devastating and far-reaching consequences not only for the nation's clinical

laboratories, but also for the nation's entire healthcare system, including the millions of vulnerable patients who depend on the essential clinical testing services that laboratories provide. FDA's final rule means that, in order to be *legally* marketed, virtually all diagnostic laboratory tests will have to undergo costly and time-consuming administrative review through a regulatory process that was designed for evaluating manufactured medical devices, not professional testing services.

6. The final rule states that FDA intends to apply this onerous regulatory regime to new and modified laboratory-developed tests, which will dramatically increase research and development costs, hinder vital medical innovation, and hamper adaptation of existing tests to meet evolving patient needs. Indeed, FDA itself has recognized "significant regulatory changes" to the treatment of laboratory testing services "could have negative effects on the public health." 62 Fed. Reg. 62,243, 62,249 (Nov. 21, 1997). With respect to unmodified existing tests, FDA states that as a matter of enforcement discretion it generally does not intend—at least not at this time—to enforce certain especially burdensome medical-device requirements, such as premarket review. But FDA's final rule means that in the agency's view all of those tests, including tests that physicians have relied on for decades, are being marketed illegally and are subject to FDA enforcement action at any time.

7. FDA does not have authority to regulate professional laboratory-

developed testing services as medical devices. The text and structure of the FDCA make plain that FDA's authority to regulate "devices," which dates to 1938 and was expanded through the Medical Device Amendments of 1976, extends only to physical products that are sold and distributed by manufacturers in interstate commerce. The FDCA has never applied medical device regulation to laboratory testing services. And for good reason: Those tests are not physical products sold and distributed by manufacturers. Instead, they are professional healthcare services offered by highly skilled and trained laboratory professionals that are outside FDA's regulatory expertise and are subject to different regulatory requirements. A laboratory-developed test is a process by which laboratory professionals use various tools—some of which may be individually regulated as devices—to derive diagnostic information that a patient and the patient's physician may use in making health care decisions.

8. Nor has FDA provided any plausible interpretation of the statute that could support its approach. FDA's assertion that laboratory testing services are devices just because the professionals performing those services *use* devices is as unreasonable as calling a surgical procedure a "device" because the surgeon uses a scalpel, or calling a doctor's physical examination a "device" because the doctor uses a stethoscope. The fact that a skilled professional may use physical tools, in addition to his or her professional

expertise, training, and judgment, to perform a procedure does not mean that the procedure itself is a device.

9. Equally untenable is FDA's contention that laboratory testing services are devices because they serve a similar function to in vitro diagnostic test kits, which FDA regulates as devices. An IVD test kit is a "device" because it is a packaged set of components manufactured and sold in interstate commerce as a single physical product, like an at-home COVID test. Such commercial test kits are fundamentally different from laboratory-developed tests, which are professional services performed by professional clinicians in a laboratory.

10. As noted above, the development and performance of laboratory-developed tests is regulated at the federal level under a separate statutory and regulatory framework—CLIA—that ensures the validity and reliability of laboratory tests and the training and qualifications of the skilled professionals who perform, supervise, and interpret those tests. Notably, when Congress enacted CLIA, it did not so much as hint that it had already granted FDA authority to regulate laboratory testing services as medical devices under the FDCA. If Congress had wanted to expand FDA's authority so dramatically over an entire profession, it would have said so.

11. In its proposed rule, FDA initially contended that nearly all existing laboratory-developed tests would have to go through a burdensome

approval or clearance process before they could continue to be used to help patients and physicians. In the final rule, recognizing that its sweeping interpretation would be unworkable and have devastating consequences, FDA tried to rewrite the FDCA in the guise of dozens of pages of vague, non-binding "enforcement discretion policies" that are designed to mitigate (but not eliminate) those consequences. This "need to rewrite" the statute "should have alerted [FDA] that it had taken a wrong interpretive turn." *Util. Air Regul. Grp.*, 573 U.S. at 328. "Agencies are not free to 'adopt … unreasonable interpretations of statutory provisions and then edit other statutory provisions to mitigate the unreasonableness.'" *Id.* (quotation marks omitted).

12. The final rule repeatedly warns that FDA may change its enforcement discretion policy at any time and bring the hammer down on laboratories for unlawfully marketing existing tests. Even if FDA never takes that step, the rule creates enormous regulatory uncertainty for laboratories and places them in an impossible position: They must either (1) withdraw all their existing tests from the market (which FDA recognized would be devastating for patients and the public health); (2) incur massive costs to obtain FDA approval or clearance for their existing tests, which would divert resources from innovating and developing new tests and overwhelm FDA; or (3) continue serving patients by providing existing tests without FDA approval or clearance, even though FDA says that by doing so they are breaking the law

and are subject to enforcement action at any time in the agency's sole discretion.

13. In addition to casting a shadow over all existing tests, the final rule undermines innovation and threatens patient access to critical new diagnostic tests. FDA lacks the expertise or resources to timely and efficiently review and approve new and modified laboratory-developed testing services. Moreover, given the need for FDA approval or clearance, the rule will discourage laboratories from devoting scarce resources to research and development, which will impede the creation of new and improved tests for cancer, infectious disease, cardiovascular disease, and countless other diseases and conditions. Because many tests do not generate sufficient revenue to support the expense of seeking FDA approval or clearance, many important tests will never be developed—especially tests for rare diseases or that serve small patient populations, such as children or racial or ethnic minorities.

14. FDA has identified no genuine public-health justification for imposing these costs on laboratories and the physicians and patients who rely on them. The agency's exercise of enforcement discretion for existing tests only underscores the lack of a valid public-health rationale for treating *any* laboratory-developed tests as medical devices.

15. For these reasons and those explained below, ACLA and HealthTrackRx seek declaratory and injunctive relief to vacate, set aside, and

enjoin enforcement of the final rule.

PARTIES

16. Plaintiff American Clinical Laboratory Association ("ACLA") is a not-for-profit association with its principal place of business in Washington, D.C. ACLA is the national trade association representing leading laboratories that deliver essential diagnostic health information to patients and providers. ACLA's members perform hundreds of millions of tests each year for patients across the country, and ACLA advocates for policies that expand access to the highest quality clinical laboratory services, improve patient outcomes, and advance the next generation of personalized care.

17. Plaintiff HealthTrackRx Indiana, Inc. is a corporation organized and existing under the laws of Indiana with its principal place of business in Denton, Texas. Plaintiff HealthTrackRX, Inc., is a corporation organized and existing under the laws of Texas with its principal place of business in Denton, Texas. HealthTrackRx is a leading national PCR-based infectious disease laboratory, providing services to over 10,000 clinicians nationwide. HealthTrackRx is also an ACLA member.

18. Defendant FDA, which has its principal office at 10903 New Hampshire Avenue, Silver Spring, Maryland 20993, is a federal agency headquartered in Maryland. It regulates drugs and medical devices under authority delegated by Congress and the Secretary of Health and Human

Services.

19. Defendant U.S. Department of Health and Human Services, which has its principal office at 200 Independence Avenue, S.W., Washington, D.C. 20201, is a federal agency headquartered in the District of Columbia. It has authority over FDA.

20. Defendant Xavier Becerra is being sued in his official capacity as Secretary of Health and Human Services. As Secretary, Mr. Becerra has ultimate responsibility for the activities of the Department of Health and Human Services, including those actions complained of herein. Mr. Becerra maintains an office at 200 Independence Avenue, S.W., Washington, D.C. 20201.

21. Defendant Robert Califf, M.D., is being sued in his official capacity as Commissioner of Food and Drugs, FDA. As Commissioner, Dr. Califf is responsible for the activities of FDA, including those actions complained of herein. Dr. Califf maintains an office at 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

JURISDICTION AND VENUE

22. This Court has original subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1331 because it arises under the laws of the United States.

23. Plaintiffs have a right to bring this action pursuant to the

Administrative Procedure Act ("APA"), 5 U.S.C. §§ 701–706, and the Declaratory Judgment Act, 28 U.S.C. § 2201.

24. Plaintiffs have standing because they or their members provide thousands of laboratory-developed tests that would be treated as devices under the final rule, making them direct objects of regulation under that rule. *See* Dr. Reddy Decl. ¶¶ 6–7, 9–14, 24–37 (attached as Ex. A); Dr. Eisenberg Decl. ¶¶ 6, 8–10, 12, 18–20 (attached as Ex. B); Dr. Fesko Decl. ¶¶ 5–11 (attached as Ex. C); Dr. Genzen Decl. ¶¶ 12–13, 16–18, 22 (attached as Ex. D); Dr. Morice Decl. ¶¶ 19, 22, 25–30 (attached as Ex. E). Plaintiffs and their members also engage in research and development efforts to bring to market new and modified tests that would be treated as devices under the final rule. *See* Dr. Reddy Decl. ¶¶ 20, 24, 32, 36–37; Dr. Eisenberg Decl. ¶¶ 6, 8, 9–10, 12, 18–19; Dr. Fesko Decl. ¶¶ 7, 9, 16, 19–21; Dr. Genzen Decl. ¶¶ 19–21, 25–42, 47–50, 58–59; Dr. Morice Decl. ¶¶ 9, 17–18, 22–26, 58.

25. There is currently an actual, justiciable controversy between the parties concerning whether FDA's final rule is consistent with the requirements of the FDCA, 21 U.S.C. § 301 *et seq.*, and the APA.

26. Venue is proper in this District pursuant to 28 U.S.C. § 1391(e) because this is a civil action in which the defendants are officers or agencies of the United States, plaintiff HealthTrackRx resides in this District, and no real property is involved in this action. *See* Dr. Reddy Decl. ¶ 8.

GENERAL ALLEGATIONS

A. Laboratory-developed tests are services carried out by highly skilled and trained laboratory professionals.

27. Laboratory-developed tests are procedures designed, developed, and performed by clinical laboratories certified to perform high-complexity testing to yield important clinical information about a patient that can be used to inform or guide patient care. *See* Dr. Reddy Decl. ¶¶ 9–17, 23; Dr. Eisenberg Decl. ¶¶ 6–10, 15; Dr. Fesko Decl. ¶¶ 5–11; Dr. Genzen Decl. ¶¶ 11–13, 15–20, 23–26, 28; Dr. Morice Decl. ¶¶ 14. 27–28, 48–52.

28. Laboratories that develop and perform these tests are providing professional healthcare services; they are not acting as device manufacturers or distributing devices. *See* Dr. Reddy Decl. ¶¶ 21–23; Dr. Eisenberg Decl. ¶¶ 14–15, 18; Dr. Fesko Decl. ¶¶ 14–15; Dr. Genzen Decl. ¶¶ 43–45; Dr. Morice Decl. ¶¶ 14, 48–56.

29. As an example, consider the steps associated with performing a mass spectrometry test offered by an ACLA member laboratory. Mass spectrometry is a chemical analysis technique with many uses, including helping manage hormonal disorders such as Cushing's syndrome and measuring proteins with functions related to cancer and Alzheimer's disease. After a physician orders the test, a blood specimen is obtained by a phlebotomist and sent to the laboratory. Laboratory staff then perform the

following tasks:

a. *Pre-analytical steps.* The laboratory receives the blood sample and enters it into the laboratory information system. Laboratory staff then complete pre-analytical steps in accordance with the relevant standard operating procedures. That may include centrifuging the sample or aliquoting the sample into a separate tube for testing.

b. *Analytical steps.* A laboratory scientist prepares reagents, standards, and quality control materials, and retrieves the patient sample for testing. The scientist pipettes the applicable samples and reagents into a 96-well plate and extracts the analytes of interest using an automated liquid handling instrument. The scientist then enters relevant information into the instrument software and loads samples onto the testing system, which includes an automated sampler, liquid chromatography instrumentation, and a high-resolution mass spectrometer. When testing is complete, the scientist reviews the test both qualitatively and quantitatively (*e.g.*, reviewing chromatography and signal-to-noise ratios), including reviewing quality control to ensure the results are within parameters for acceptable performance. The scientist then reviews the patient results, uses software to determine the concentration of the analyte(s) being measured, and enters the results into the laboratory information system.

c. *Post-analytical steps.* A second laboratory scientist or lead

scientist reviews the results to confirm they were accurately interpreted, quantitated, and entered into the laboratory information system. The reviewing scientist approves the results, sending them to the patient's electronic medical record. The ordering physician then reviews the laboratory result produced by the test and uses it to inform patient care decisions.

30. This is a laboratory-developed testing service: a series of processes and tasks undertaken by trained laboratory professionals using instruments and other tools to derive information that may be useful to a treating physician. Under any reasonable interpretation, these procedures and the exercise of judgment that they require constitute a professional service, not a manufactured device. *See* Dr. Reddy Decl. ¶¶ 14, 22–23; Dr. Fesko Decl. ¶¶ 15, 20; Dr. Eisenberg Decl. ¶¶ 8, 14–15, Dr. Genzen Decl. ¶¶ 43–45; Dr. Morice Decl. ¶¶ 14, 48–56.

31. Laboratory-developed tests are a vital part of the U.S. healthcare system and make significant contributions to patient care. They have often been responsible for scientific innovations and breakthroughs—for example, testing for the BRCA1/BRCA2 genetic mutations that indicate susceptibility to breast and ovarian cancer—that have become part of the standard of care (and in some cases, have been incorporated into FDA-cleared or approved IVD test kits). They also play a critical role in responding to public health threats from rare or emerging pathogens and new synthetic drugs, such as fentanyl analogs.

32. Many important diagnostic tests are available *only* as laboratory-developed testing services because no FDA-cleared or approved test kit exists for a particular disease, condition, or patient population. And even when an approved or cleared test kit is available, laboratory-developed tests often perform better and are preferred by physicians. Unlike medical devices, which must always take their approved form, laboratory-developed tests can be updated and customized (under the supervision of a CLIA-qualified laboratory director) to take account of the latest scientific developments and the needs of particular patients and clinicians. *See* Dr. Reddy Decl. ¶¶ 17, 36–37; Dr. Genzen Decl. ¶¶ 26–27.

B. FDA's statutory authority to regulate medical devices does not extend to professional services.

33. The FDCA was originally enacted by Congress in 1938. It authorized FDA to regulate "foods," "drugs," "devices," and "cosmetics," all of which were physical *products* that were mass-manufactured and commercially distributed. *See* Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, § 201(h), 52 Stat. 1040, 1041 ("The term 'device' … means instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals."); *see also id.* §§ 201(f), (g),

(i), 52 Stat. at 1040–41 (defining "food," "drug," and "cosmetic," respectively).

34. Congress greatly expanded FDA's authority over devices in the Medical Device Amendments of 1976 ("MDA"), Pub. L. No. 94-295, 90 Stat. 539, which amended the FDCA to "impose[] a regime of detailed federal oversight" on medical devices. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 316 (2008).

35. The FDCA's Medical Device Amendments classify medical devices into three categories based on the level of risk they present. Class I devices are subject only to "general controls" such as labeling requirements. Class II devices are also subject to "special controls" such as performance standards and postmarket surveillance measures. Class III devices are subject to "a rigorous regime of premarket approval." *Id.* at 316–17 (quotation marks omitted); *see* 21 U.S.C. § 360c(a)(1).

36. There are a few statutory exceptions to these general rules. Class III devices that were marketed before the statute's effective date in 1976 were allowed to remain on the market unless and until FDA promulgates a regulation requiring the submission of premarket approval applications. *Riegel*, 55 U.S. at 316–17; *see* 21 U.S.C. §§ 360c(f)(1), 360e(b)(1). Moreover, a new Class III device need not go undergo full premarket approval if FDA finds that the new device is "substantially equivalent" to a grandfathered device. 21 U.S.C. § 360c(f)(1)(A).

37. While the three device categories differ by level of risk, they all

comprise tangible, physical products. For example, Class I devices include "elastic bandages and examination gloves," Class II devices include "powered wheelchairs and surgical drapes," and Class III devices include "replacement heart valves, implanted cerebella stimulators, and pacemaker pulse generators." *Riegel*, 552 U.S. at 316–17.

38. The statutory definition of "device" makes clear that FDA's regulatory jurisdiction under the FDCA is limited to physical products and does not encompass professional services. The statute provides:

> The term "device" … means an *instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory*, which is—
>
> > (A) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
> >
> > (B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
> >
> > (C) intended to affect the structure or any function of the body of man or other animals, and
>
> which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

21 U.S.C. § 321(h)(1) (emphasis added).

39. All of the terms used in the FDCA's definition of "device"—

"instrument," "apparatus," "implement," "machine," "contrivance," "implant," and "in vitro reagent"—refer to tangible, physical objects. Moreover, the statute uses the term "article" as a catch-all to encompass all "devices," and the plain meaning of "article" does not include intangible services. An "article" is a "particular material thing, esp. one belonging to a specified class; a commodity; an item of goods or property." *Article*, Oxford English Dictionary (2023), https://www.oed.com/search/dictionary/?scope=Entries&q=article. Consistent with this common definition, courts have consistently construed the term "article" to mean a "material thing" or a "tangible item." *See, e.g.*, *ClearCorrect Operating, LLC v. ITC*, 810 F.3d 1283, 1290–94 (Fed. Cir. 2015) (construing the term "articles" in the Tariff Act), *reh'g en banc denied*, 819 F.3d 1334 (Fed. Cir. 2016) (mem.).

40. Other provisions of the FDCA confirm that a "device" is a physical product, not a service. Several key provisions are triggered only when a device is shipped or received in interstate commerce, commercially distributed, or held for sale—actions that, in ordinary parlance, can be performed on a tangible article but not on an intangible professional service.

41. For example, section 510(k) of the FDCA requires a device manufacturer to file a premarket notification report with FDA at least 90 days before "the introduction or delivery for introduction into interstate commerce for commercial distribution of a device." 21 U.S.C. § 360(k). "Commercial

distribution" is defined in an FDA regulation to mean "any distribution of a device intended for human use which is held or offered for sale." 21 C.F.R. § 807.3(b). Similarly, section 301(k) prohibits various acts "with respect to" a device "if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded." 21 U.S.C. § 331(k). None of these provisions can reasonably be applied to an intangible professional service performed within a laboratory.

42. Still other provisions of the FDCA discuss devices in ways that make sense only if applied to physical products. For example, an application for premarket approval for a device must include, among other things: (i) a description of "the components, ingredients, and properties" of the device; (ii) a description of the methods, facilities and controls used in "the manufacture, processing, and, when relevant, packing and installation" of the device; and (iii) "such samples of such device and of components thereof as the Secretary may reasonably require" or "information concerning the location of one or more such devices readily available for examination and testing." 21 U.S.C. § 360e(c)(1)(B), (C), (E). Intangible professional services do not have components, ingredients, or properties; the services are not manufactured, processed, packed, or installed (even if providing them might entail using a manufactured product or products); and samples of a service cannot be

submitted to FDA or made readily available for inspection. *See* Dr. Reddy Decl. ¶¶ 22–23; Dr. Eisenberg Decl. ¶¶ 14–15; Dr. Fesko Decl. ¶ 15; Dr. Genzen Decl. ¶ 45; Dr. Morice Decl. ¶¶ 14, 48–56.

43. So too, the statute provides that in certain circumstances FDA may order the manufacturer, importer, or distributor of a device to "repair the device" or "replace the device with a like or equivalent device." 21 U.S.C. § 360h(b). Unlike physical products, intangible professional services cannot be repaired or replaced.

44. Several of FDA's promulgated regulations for devices can similarly be understood only as applied to a manufactured product. For example, an FDA regulation requires the "label of every medical device" and "[e]very device package" to bear a unique device identifier. 21 C.F.R. § 801.20(a). "Label" is defined as "a display of written, printed, or graphic matter upon the immediate container of any article," and "device package" is defined as "a package that contains a fixed quantity of a particular version or model of a device." *Id.* § 801.3 (incorporating 21 U.S.C. § 321(k)). These requirements make sense in the context of manufactured devices, where the primary and expected means of communication between the manufacturer and any purchaser is through a standardized label. In sharp contrast, a laboratory scientist's performance of the tasks comprising a laboratory-developed test cannot be "labeled" or "packaged" in compliance with these regulations. Nor can those professional

services be summarized in a standardized label; instead, clinical laboratory services entail the exercise of professional judgment when interpreting testing results and often a consultation process between professional laboratory clinicians and doctors and other healthcare providers. *See* Dr. Eisenberg Decl. ¶ 14; Dr. Fesko Decl. ¶¶ 9, 15; Dr. Genzen Decl. ¶ 19; Dr. Morice Decl. ¶¶ 27, 48–56.

45. Viewed collectively, these provisions confirm what the statutory definition of "device" makes clear: A "device" under the FDCA is a physical product or manufactured good, not an intangible professional service.

C. Congress created a separate and distinct framework for regulating laboratory testing services.

46. Congress created a separate statutory and regulatory framework to regulate laboratory testing services: the Clinical Laboratories Improvement Act of 1967, Pub. L. No. 90-174, § 5, 81 Stat. 533, 536, which was significantly expanded by the Clinical Laboratory Improvement Amendments of 1988, Pub. L. No. 100-578, 102 Stat. 2903, codified at 42 U.S.C. § 263a. This statutory framework is commonly referred to as "CLIA."

47. Congress's enactment and expansion of CLIA in 1967 and 1988 confirms that it did not understand the Medical Device Amendments in 1976 as authorizing FDA to regulate laboratory testing services as medical devices.

48. CLIA establishes a framework for the regulation of laboratories

and laboratory testing services. Within the Department of Health and Human Services, responsibility for administering CLIA belongs primarily to the Centers for Medicare and Medicaid Services ("CMS"), which has issued extensive implementing regulations. *See generally* 42 C.F.R. Part 493.

49. CLIA and its implementing regulations reflect that performing and interpreting laboratory tests requires significant scientific and technical knowledge, training, experience, and judgment, and is fundamentally different from manufacturing physical devices. *See* Dr. Reddy Decl. ¶ 22; Dr. Genzen Decl. ¶ 27; Dr. Morice Decl. ¶¶ 12, 49, 52, 56–58, 62; Dr. Eisenberg Decl. ¶¶ 15–16; Dr. Fesko Decl. ¶ 15.

50. Under CLIA, all laboratories that perform clinical tests on human specimens must be certified by CMS or accredited through certain CMS-approved accreditation organizations. 42 U.S.C. § 263a(b); *see* Dr. Reddy Decl. ¶ 12; Dr. Genzen Decl. ¶ 15. Both CMS and accreditation organizations issue standards to assure that laboratories' performance is "consistent" and their tests are "valid and reliable," including quality-control standards and standards for the qualifications of the personnel directing, supervising, and performing the tests. 42 U.S.C. § 263a(f)(1). The standards must take into account, among other things, the type of tests performed, the "degree of independent judgment involved," "the amount of interpretation involved," "the difficulty of the calculations involved," and "the type of training required."

§ 263a(f)(2).

51. The College of American Pathologists is the most prominent example of a CMS-approved accreditation organization, and to be accredited by that organization, a laboratory must be inspected initially and then every two years and must demonstrate that it complies with approximately 3,000 specific requirements, including validation of any clinical claims made by the laboratory for any laboratory-developed testing service. *See* College of American Pathologists, *CAP Advances Quality in Laboratory Medicine and Safeguards Patient Testing with Annual Release of Laboratory Accreditation Program Checklists* (Sept. 23, 2021), https://newsroom.cap.org/cap-in-the-news/cap-advances-quality-in-laboratory-medicine-and-safeguards-patient-testing-with-annual-release-of-la/s/88c2ad6c-72b4-4641-aaa7-3edb4954aac8.

52. The CLIA regulations ensure that laboratory testing services are performed only by highly skilled and trained laboratory professionals. Laboratories that perform high-complexity tests must be overseen by a laboratory director, who must either be a licensed physician or hold a doctoral degree in a chemical, physical, biological, or clinical laboratory science. 42 C.F.R. § 493.1443. The laboratory director is responsible for ensuring that the laboratory's test methodologies are "capab[le] of providing the quality of results required for patient care," that "[l]aboratory personnel are performing the test methods as required for accurate and reliable results," and that "consultation

is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific patient conditions." *Id.* § 493.1407(e)(3), (9).

53. The laboratory must also have a technical supervisor with appropriate training or experience for the types of tests performed by the laboratory, *id.* § 493.1449, and a clinical consultant qualified to "consult with and render opinions to the laboratory's clients concerning the diagnosis, treatment, and management of patient care," *id.* § 493.1455. The clinical consultant is responsible for providing "consultation regarding the appropriateness of the testing ordered and interpretation of test results." *Id.* § 493.1457. And all laboratory personnel who perform high-complexity tests must either be licensed physicians or have appropriate training and experience in laboratory science or medical technology. *Id.* § 493.1489.

54. Under CLIA, laboratory testing services are subject to strict quality controls. When a laboratory introduces a new diagnostic test "not subject to FDA clearance or approval" (or when it modifies an FDA-cleared or approved IVD test kit purchased from a device manufacturer), it must, "before reporting patient test results," establish "performance specifications" for the test—including specifications for accuracy, precision, analytical sensitivity, and other characteristics "required for test performance." *Id.* § 493.1253(b)(2). Performance of the test is also subject to the laboratory's CLIA-mandated

quality control system, which requires, among other things, establishment and performance of calibration and control procedures; maintenance and function checks for equipment, instruments and test systems; and ongoing quality monitoring. *Id.* § 493.1200–1299.

55. CLIA further requires laboratories to demonstrate proficiency in their tests multiple times a year. 42 U.S.C. § 263a(f)(3). For many of their tests, laboratories must enroll and participate in approved proficiency testing programs, which serve as external quality control checks for every test the laboratory performs. Proficiency testing requires that the laboratory test blinded samples according to its typical procedures and report the results back to the testing program for evaluation. 42 C.F.R. § 493.801. A laboratory that fails to achieve satisfactory proficiency scores may face sanctions, including suspension, limitation, or revocation of its CLIA certificate. *Id.* §§ 493.803(b), 493.1806.

56. CLIA-certified laboratories are subject to inspections, by the Department of Health and Human Services, state agencies, and authorized accrediting bodies. *See, e.g.,* 42 U.S.C. § 263a(g); 42 C.F.R. Part 493, Subpart Q.

57. Although CLIA was enacted nine years before the Medical Device Amendments and significantly expanded twelve years after those Amendments, neither CLIA nor its legislative history acknowledges any

authority of FDA to regulate laboratory testing services as medical devices.

58. The Senate Report on the 1967 bill addressed concerns about possible overlap between regulation of clinical laboratories under CLIA and under the Medicare statute, but it did not mention any role for FDA. *See* S. Rep. No. 90-724 (1967), *reprinted in* 1967 U.S.C.C.A.N. 2076, 2084.

59. Likewise, the House Report on the 1988 bill described "[t]he Current Regulatory System" as involving federal regulation of laboratories "under two programs"—the Clinical Laboratory Improvement Act of 1967 and the Medicare statute—and did not so much as mention regulation by FDA. H.R. Rep. No. 100-899, at 11 (1988). The Report also states that the purpose of CLIA was to replace a "confusing" system where laboratories were regulated under "two separate and distinct statutes" with a single "unified regulatory mechanism"—a purpose that is at odds with subjecting laboratory testing services to regulation under both CLIA and the FDCA. *Id.* at 12.

60. In short, there is no indication that Congress, when it enacted CLIA, believed that clinical laboratories' provision of testing services was already subject to regulation under the FDCA.

D. FDA has never broadly regulated laboratory testing services as medical devices.

61. In the nearly half-century since Congress enacted the Medical Device Amendments of 1976—not to mention the 86 years since Congress first

gave FDA authority over medical devices in 1938—FDA has never before acted to broadly regulate laboratory-developed tests as "devices" under the FDCA. This lengthy history confirms that FDA lacks statutory authority to do so now. *See Util. Air Regul. Grp.*, 573 U.S. at 324 (an agency's reliance on "a long-extant statute" to bring about a dramatic "expansion in [its] regulatory authority" should be met with "skepticism"); *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 157–58 (2012) (when an agency has responded to an industry's "decades-long practice" with a "lengthy period of conspicuous inaction," the likely explanation is that the industry practice was lawful).

1. FDA's Many Years of Silence

62. In the first 16 years following Congress's enactment of the Medical Device Amendments to the FDCA, from 1976 through 1992, FDA did not claim any authority to regulate laboratory testing services as "devices." Nor had FDA ever claimed such authority under the FDCA as enacted in 1938, even though that statute contained a similar definition of "device."

63. Clinical laboratories thus reasonably understood that their services were not subject to regulation under the FDCA. *See* Dr. Reddy Decl. ¶ 24; Dr. Eisenberg Decl. ¶¶ 15–17; Dr. Fesko Decl. ¶ 14; Dr. Genzen Decl. ¶ 46. Congress acted on the same understanding when it enacted CLIA to create a single, unified, comprehensive system for the federal regulation of laboratory testing.

64. The first time FDA suggested that it might possess authority to regulate laboratory-developed tests as devices was in 1992—16 years after Congress enacted the Medical Device Amendments and 54 years after it first enacted the FDCA. But when that suggestion drew immediate and strenuous objections, FDA essentially backed down and announced a "policy" of not exercising jurisdiction over laboratory testing services that it adhered to for the next 30 years.

65. In its final rule, FDA cites a 1973 rulemaking as purported evidence that FDA treated tests as devices before Congress enacted the Medical Device Amendments. 89 Fed. Reg. 37,286, 37,328 (May 6, 2024) (citing 38 Fed. Reg. 7096 (Mar. 15, 1973)). That rulemaking defined "[i]n vitro diagnostic *products*"—not services—as diagnostic "reagents, instruments and systems." 38 Fed. Reg. at 7098. (emphasis added). Although FDA now suggests that the term "systems" was intended to include testing services, the context makes clear that the only "systems" subject to the rule were finished products, not laboratory tests. For example, the 1973 rule included labeling provisions requiring that certain information be affixed to the "retail package" of the "article." 38 Fed. Reg. at 7098. The 1973 rule thus confirms that FDA originally sought to regulate only physical products, not professional laboratory procedures or techniques. Moreover, when Congress amended the definition of "device" in 1976, it did not include the term "system" or even the term "in vitro

product," but only the narrower term "in vitro reagent."

2. FDA's Never-Finalized 1992 Guidance

66. Sixteen years following the enactment of the Medical Device Amendments, in 1992, in a draft Compliance Policy Guide, FDA made the novel claim that it could regulate laboratory-developed tests as medical devices. This claim was made in passing in a document that generally addressed the marketing and distribution of IVD test kits. In a brief aside, FDA stated that "laboratories have been manufacturing 'home brew' products, either from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes," and added that "[t]hese products are subject to the same regulatory requirements as any unapproved medical device." FDA, Draft Compliance Policy Guide: Commercialization of Unapproved *In Vitro* Diagnostic Devices Labeled for Research and Investigation at 4 (Aug. 3, 1992).

67. The laboratory profession immediately objected to this abrupt and unexplained assertion of jurisdiction over professional laboratory testing services. For example, a law firm that represented clinical laboratories filed a citizen petition asking FDA not to assert jurisdiction over laboratories' "in-house assays" and noting, among other concerns, that FDA's authority over medical devices "does not extend to test methods, protocols, or services." Citizen Pet. at 9, Hyman, Phelps & McNamara, P.C., Docket No. FDA-92-P-

0405 (Oct. 22, 1992) ("1992 Citizen Petition").

68. FDA did not immediately respond to the 1992 Citizen Petition. But following controversy over the 1992 draft guidance, FDA did not finalize that guidance or attempt to actively regulate laboratory testing services. Instead, FDA sought to calm the waters by announcing that it did "not intend to routinely exercise its authority over home-brew tests." *IVD Policy Will Not Include Exemptions for "Standard-of-Care" Tests*, THE GRAY SHEET (Oct. 11, 1993).

3. FDA's Sporadic Claims of Authority in the 1990s and 2000s

69. FDA next asserted that it had jurisdiction over laboratory testing services in the non-binding preamble to a 1996 proposed rule regarding device classification levels for certain "active ingredients used in preparing in-house developed [laboratory] tests." 61 Fed. Reg. 10,484, 10,485 (Mar. 14, 1996). In the preamble, FDA noted that it had previously regulated as devices only (i) "diagnostic tests that are traditionally manufactured and commercially marketed as finished products" (*i.e.*, test kits), and (ii) tangible articles used as test "ingredients," such as "laboratory apparatus" and "chemicals or antibodies," that laboratories "purchase from biological or chemical suppliers." *Id.* at 10,484.

70. In response, ACLA and other stakeholders filed comments

challenging FDA's assumption that it had authority to regulate laboratory testing services as medical devices.

71. In the preamble to the final rule, FDA stated that it "believes that clinical laboratories that develop such [in-house] tests are acting as manufacturers of medical devices." 62 Fed. Reg. at 62,249. FDA recognized, however, that "the use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes to this area could have negative effects on the public health." *Id.* FDA therefore stated that it would continue to focus on regulating "ingredients … that move in commerce" and other tangible articles, not laboratory testing services. *Id.*; *see id.* at 62,250 (concluding that "regulation of all in-house developed tests" was not "appropriate at this time").

72. Over the next 12 years, FDA continued to assert periodically and in draft non-binding guidance that it had statutory authority to regulate professional laboratory testing services as manufactured devices but was choosing not to. But FDA never took any final regulatory action backing up its non-binding statements. And the agency's consistent policy of *not* treating laboratory-developed tests as devices made these occasional claims nothing but empty posturing.

4. FDA's Never-Finalized 2014 Guidance

73. FDA's first real suggestion that it might put its posturing into

practice came in 2010, when the agency announced its intention to "reconsider its policy of enforcement discretion" with respect to laboratory-developed tests. 75 Fed. Reg. 34,463–64 (June 17, 2010). FDA said it intended to "develop a draft oversight framework for public comment" that would "phase in … over time based on the level of risk" presented by various tests. *Id.*

74. In response, ACLA submitted comments reiterating that "laboratories are providers of testing services; they are not medical device manufacturers." ACLA Supp. Comments on Oversight of Lab'y Developed Tests at 4, Docket No. FDA-2010-N-0274 (Sept. 15, 2010). ACLA explained that, while it might be appropriate for FDA to regulate as devices "the *products* used by clinical laboratories to perform tests," including "commercially distributed *in vitro* diagnostic test kits," FDA should not and cannot recklessly impose device regulation on the provision of "laboratory *services*." *Id.* at 4, 6 (emphases added).

75. Two years later, with FDA still not having published any proposed oversight framework, Congress prohibited the agency from issuing "any draft or final guidance on the regulation of laboratory-developed tests" for five years unless the details of FDA's plan were disclosed to the relevant congressional committees at least 60 days prior to such issuance. Pub. L. No. 112-144, § 1143(a), 126 Stat. 993, 1130 (2012).

76. A year after that, ACLA submitted a citizen petition asking FDA

to acknowledge that laboratory testing services are not devices. ACLA's petition explained that text and legislative history make clear that "devices" are tangible articles and do not include services or procedures. *See* ACLA Citizen Pet. at 7–9, Docket No. FDA-2013-P-0667 (June 4, 2013). The petition acknowledged that performing a laboratory-developed test "might involve use of" physical devices, such as "reagents," "laboratory equipment," or "IVD test kits." *Id.* at 1, 8. But it stressed that a clinical service does not become subject to regulation as a device "simply because the service involves the use of tangible articles which may be subject to FDA regulation." *Id.* at 8–9. Otherwise, it noted, "every surgical procedure or physical examination that is performed on a patient using tangible devices" would itself be a "device." *Id.*

77. FDA denied ACLA's citizen petition in 2014 and asserted that laboratory-developed tests "are 'devices' as defined in the FDCA." FDA Denial of ACLA Citizen Pet. at 3, Docket No. FDA-2013-P-0667 (July 31, 2014). Eliding the distinction between professional services and physical products, FDA claimed that laboratory testing services are devices because they *make use of* various physical "articles," such as "reagents," "instruments," and "equipment"—even though the testing services themselves are plainly not "articles." *Id.* at 3–5, 23.

78. On the same day it denied ACLA's citizen petition, FDA made similar assertions in response to two other citizen petitions, which had been

pending since 2006 and 2008, respectively. *See* FDA Denial of Wash. Legal Found. Citizen Pet. at 3–4, Docket No. FDA-2006-P-0149 (July 31, 2014); FDA Denial of Genentech, Inc., Citizen Pet. at 5–6, Docket No. FDA-2008-P-0638 (July 31, 2014). Also on that day, FDA notified Congress of its intent to issue draft guidance documents regarding laboratory-developed tests.

79. On October 3, 2014, FDA released the draft guidance documents it had promised in 2010, proposing to phase in new regulation of laboratory-developed tests as devices over a nine-year period. In announcing the draft guidance documents, FDA described laboratory-developed tests as "a subset of in vitro diagnostic devices that are intended for clinical use and designed, manufactured, and used within a single laboratory." 79 Fed. Reg. 59,776, 59,777 (Oct. 3, 2014); *see also* 79 Fed. Reg. 59,779, 59,780 (Oct. 3, 2014).

80. ACLA submitted comments on the draft guidance documents. Among other points, ACLA's comments explained once again that "a 'device' is a physical article or product" and "[l]aboratory-developed testing services are processes and methodologies that are qualitatively and categorically different from the tangible goods that FDA may regulate as 'devices.'" ACLA Comments on Oversight of Laboratory Developed Tests and Reporting at 5, Docket Nos. FDA-2011-D-0357 & -0360 (Feb. 2, 2015). ACLA also reiterated that "[l]aboratory-developed testing services do not become medical devices merely because they sometimes utilize other medical devices," such as reagents and

laboratory equipment. *Id.* at 6. As ACLA noted, "every time a radiologist reads an x-ray, she is providing a service that depends on a medical device—the x-ray machine. However, the radiologist is rendering a service and is not subject to regulation under the FDCA" as a device manufacturer. *Id.*

81. On November 18, 2016, FDA backed down, announcing that it would not finalize the 2014 draft guidance documents. In a white paper published in January 2017, FDA noted that it had made this decision "to allow for further public discussion on an appropriate oversight approach, and to give our congressional authorizing committees the opportunity to develop a legislative solution." FDA, Discussion Paper on Laboratory Developed Tests (LDTs) at 1 (Jan. 13, 2017).

5. The 2020 Charrow Memo Questions FDA's Authority to Regulate Laboratory Testing Services

82. In 2020, Robert Charrow, then-General Counsel of the Department of Health and Human Services, issued a memorandum regarding "Federal Authority to Regulate Laboratory Developed Tests."

83. The Charrow memorandum is significant because it addresses and undermines key premises upon which FDA now relies. For example, it recognized that laboratory-developed tests "were never mentioned in the [Medical Device Amendments], in the House Report accompanying it, or during the floor debates." Mem. from Robert Charrow, Gen. Counsel, to Stephen

Hahn, M.D., Comm'r of Food & Drugs, at 3 (June 22, 2020) (attached as Ex. F). It further noted that Congress's enactment of CLIA in 1988, and the Secretary's issuance of "comprehensive rules governing clinical laboratories" pursuant to CLIA, "appeared to have occupied the field for regulating [laboratory-developed tests]." *Id.* at 3–4.

84. Contrary to FDA's claims that it regarded laboratory-developed tests to be devices as far back as 1976, the Charrow memorandum acknowledges that FDA had "first suggested that [laboratory-developed tests] are subject to its jurisdiction" in 1992—16 years after the Medical Device Amendments were enacted—and that from 1992 until 2014, "FDA did little to regulate LDTs." *Id.* at 4. Moreover, although FDA had proposed altering that status quo in 2014 when it published the draft guidance documents, it had subsequently declined to finalize those documents. *Id.* at 5.

85. Acknowledging the argument that laboratory-developed tests "are not physical embodiments, *e.g.* 'contraptions,' but rather are processes or services, and therefore not devices," the Charrow memorandum observed that while "*in vitro* reagents are devices, … that does not necessarily lead to the conclusion that [laboratory-developed tests] fall within FDA's jurisdiction." *Id.* at 6. The memorandum explained that Congress's enactments do not "lead[] to the conclusion that [laboratory-developed tests] are devices" and "the Secretary has issued rules implementing Medicare and CLIA that strongly

suggest that [laboratory-developed tests] are not devices and not within FDA's jurisdiction." *Id.* at 14.

86. The memorandum also recognized that laboratory-developed tests are not "goods or commodities" but rather "clinical laboratory services," and are treated as such by Medicare. *Id.* at 10. The memorandum analogized "the development and use of" laboratory-developed tests to a "doctor's development and use of a medical procedure." *Id.*

6. Congress Chooses Not to Enact Legislation

87. Reflecting the lack of statutory authority for FDA to regulate laboratory testing services under the FDCA, Congress considered legislative proposals that would have given FDA such authority. On March 5, 2020, the VALID Act was introduced in both houses of Congress. *See* Verifying Accurate Leading-edge IVCT Development Act of 2020, H.R. 6102, 116th Cong. (2020) (companion bill S.3404). The Act would have created a new regulatory pathway, separate from both drugs and devices, for FDA premarket review and regulation of "in vitro clinical tests," including laboratory-developed tests. *See id.* § 2(a).

88. Commentators noted that "[e]arlier versions of the proposed VALID Act had been circulating in Washington for several years" following FDA's "abortive" attempt to regulate laboratory-developed tests in 2014, which FDA had "abandoned" in 2016 "amid questions about [its] jurisdiction to

regulate laboratory services." Barbara J. Evans & Ellen Wright Clayton, *Deadly Delay: The FDA's Role in America's COVID-Testing Debacle*, 130 Yale L.J. Forum 78, 83–84 (2020)).

89. The VALID Act did not pass during the 116th Congress. It was reintroduced in the 117th Congress, where it again failed to pass. *See* VALID Act of 2021, H.R. 4128, 117th Cong. (2021) (companion bill S.2209). It was introduced again in 118th Congress, and once again it failed to become law. *See* VALID Act of 2023, H.R. 2369, 118th Cong. (2023) (companion bill S.2496).

E. FDA now seeks for the first time to classify virtually all laboratory testing services as medical devices.

1. The 2023 Proposed Rule

90. With no congressional authorization forthcoming, FDA once again announced its intent to move forward with regulating virtually all laboratory-developed testing services as medical devices. FDA published its proposed rule in October 2023. *See* 88 Fed. Reg. 68,006 (Oct. 3, 2023).

91. In the proposed rule, FDA stated that it would amend a regulatory definition of "in vitro diagnostic products" to add the underlined language:

> [In vitro diagnostic products] are defined as "those 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. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body." … These products are

> devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act, including when the manufacturer of these products is a laboratory.

See id. at 68,017, 68,031 (proposed amendment to 21 C.F.R. § 809.3(a)). In the preamble, FDA made clear that it intended this amendment to signify that all laboratory testing services are "devices" and that whenever a laboratory scientist or technician performs a clinical laboratory test, he or she is engaged in "manufacturing" a "device." *Id.* at 68,007–09, 68,017–19.

92. In the preamble to the proposed rule, FDA also stated its intent to "phase out its general enforcement discretion approach" so that most laboratory-developed tests would "fall under the same enforcement approach as other" medical devices within a few years. *Id.* at 68,007.

93. FDA also recognized that its rule would impose vast costs on the clinical laboratory sector (although again, its projections were low). It estimated that the up-front cost of preparing and submitting premarket approval applications, premarket notifications, and de novo classification requests *for existing tests alone* would exceed $35 billion and could be as high as $113 billion. FDA, Docket No. FDA-2023-N-2177, Laboratory Developed Tests Proposed Rule: Preliminary Regulatory Impact Analysis at 85 (Oct. 3, 2023). It also estimated that going forward, the annual compliance for affected laboratories would be more than $4 billion and could be as high as $14 billion.

Id.; *see also* Dr. Genzen Decl. ¶¶ 54–60 (explaining why FDA's analysis "overestimates the financial benefit to society" and "understates the costs").

94. FDA acknowledged that these costs would cause some existing tests to "come off the market" because laboratories would not be able to justify the high costs of obtaining the necessary approval or clearance for those tests. 88 Fed. Reg. at 68,014.

2. ACLA's Comments on the Proposed Rule

95. FDA received more than 6,000 comments on its proposed rule, a volume of public input that reflects the radical and transformative nature of FDA's proposal.

96. ACLA submitted its comments on December 4, 2023. Among other critical points, ACLA's comments explained, yet again, that FDA does not have legal authority to regulate laboratory-developed tests as devices—including because "devices" under the FDCA are physical products that are sold and distributed by manufacturers, whereas laboratory-developed tests are services offered by trained laboratory professionals that are regulated under CLIA's distinct statutory and regulatory framework. *See* ACLA Comments on Proposed Rule "Medical Devices; Laboratory Developed Tests" at 59–71, Docket No. FDA-2023-N-2177 (Dec. 4, 2023) (attached as Ex. G). ACLA's comments also explained that FDA's unlawful assertion of jurisdiction over clinical laboratory services would seriously harm patients by undermining

diagnostic and medical innovation and limiting or eliminating access to critical tests. *Id.* at 7–18.

97. In addition, ACLA's comments demonstrated that FDA had vastly underestimated the costs of regulating laboratory-developed tests as devices—including by underestimating the number of affected laboratories, the number of currently available tests that would require costly and time-consuming premarket submissions, the cost of preparing those submissions, and the cost of complying with other device regulations. *Id.* at 46–54. And conversely, ACLA showed that FDA had vastly *overestimated* the benefits of its novel regulatory approach, including by using cherry-picked, anecdotal, and unverified "evidence" to paint an unfairly disparaging picture of laboratory testing services, while ignoring studies showing that laboratory-developed tests perform at least as well as FDA-approved or cleared IVD test kits. *Id.* at 36–46, 54–59.

3. The 2024 Final Rule

98. FDA published the final rule on May 6, 2024.

99. As contemplated in the proposed rule, FDA amended the regulatory definition of "in vitro diagnostic products" in 21 C.F.R. § 809.3(a) to add the language, "including when the manufacturer of these products is a laboratory." 89 Fed. Reg. at 37,286–87. And, as in the proposed rule, FDA made clear that it considers the provision of laboratory-based testing services a form

of device "manufacturing." *See id.* at 37,286–87, 37,289, 37,293, 37,328–32, 37,344.

100. In a major departure from the proposed rule, however, the preamble to the final rule states that FDA intends—for now and until it changes its mind—to exercise "enforcement discretion" for some or all requirements with respect to broad categories of laboratory-developed tests, including nearly all existing tests. *Id.* at 37,294–95. These non-binding "enforcement discretion policies" include the following:

- FDA will generally not enforce premarket review and Quality System ("QS") requirements for existing tests that are not modified or that are "modified in certain limited ways."
- FDA will generally not enforce premarket review requirements for tests approved by the New York State Department of Health's Clinical Laboratory Evaluation Program.
- FDA will generally not enforce premarket review and QS requirements (except certain recordkeeping requirements) for tests "manufactured and performed" by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.
- FDA will generally not enforce premarket review and QS requirements (except certain recordkeeping requirements) for non-molecular antisera tests for rare red blood cell antigens where such tests are "manufactured and performed" in blood establishments, including transfusion services and immunohematology laboratories, and where there is no alternative available to meet the patient's need for a compatible blood transfusion.
- FDA will generally not enforce any requirements for "1976-Type LDTs" (tests with certain characteristics that FDA says were common among laboratory-developed tests offered in 1976).

- FDA will generally not enforce any requirements for Human Leukocyte Antigen tests that meet certain specified characteristics.
- FDA will generally not enforce any requirements for tests intended solely for forensic (law enforcement) purposes.
- FDA will generally not enforce any requirements for tests "manufactured and performed" within the Department of Defense or the Veterans Health Administration.

Id.

101. These extensive carveouts are necessary, the final rule acknowledges, because "expecting compliance with full [quality system] and premarket review requirements for all currently marketed" laboratory-developed tests "could lead to the loss of access to safe and effective" tests "on which patients currently rely." *Id.* at 37,293; *see* Dr. Reddy. Decl. ¶ 6; Dr. Genzen Decl. ¶¶ 47, 56; Dr. Morice Decl. ¶¶ 15–16, 59–65.

102. In other words, faced with the impracticality and catastrophic impact of its novel interpretation of the law, FDA did not take that unworkability as a hint that its interpretation might be mistaken. Instead, to try to contain the damage, FDA effectively used a non-binding regulatory preamble to write a new statute on the fly, under the guise of "enforcement discretion policies."

103. These broad carveouts undermine FDA's legal rationale for the rule, which classifies all laboratory-developed tests as manufactured "devices" subject to the full suite of medical-device requirements regardless of whether

the tests fall into the categories outlined in the enforcement discretion policies. For example, FDA does not identify any textual basis in the statute for subjecting new tests to a different regime than existing tests.

104. The broad carveouts are also inconsistent with FDA's public-health rationale for the rule. For example, FDA cannot explain why, on the one hand, more limited regulation is sufficient for the tens of thousands of laboratory-developed tests in existence at the time of the final rule, but on the other hand, virtually every test developed *after* May 6, 2024, must run the full gauntlet of the medical-device requirements.

105. The final rule states that FDA will phase out its "general enforcement discretion approach" within a four-year period. 89 Fed. Reg. at 37,294. As a result, excepting the "enforcement discretion policies" described above, FDA will begin enforcing medical-device requirements with respect to laboratory-developed tests in five stages measured from the date of publication of the final rule:

- ***After 1 year***, FDA will expect compliance with medical device reporting ("MDR") requirements, correction and removal reporting requirements, and some QS requirements under 21 C.F.R. § 820.198.
- ***After 2 years***, FDA will expect compliance with requirements not covered during other stages of the phaseout policy, including registration and listing requirements, labeling requirements, and investigational use requirements.
- ***After 3 years***, FDA will expect compliance with other QS requirements under 21 C.F.R. § 820.198.

- ***After 3½ years***, FDA will expect compliance with premarket review requirements for "high-risk IVDs offered as LDTs."
- ***After 4 years***, FDA will expect compliance with premarket review requirements for "moderate-risk and low-risk IVDs offered as LDTs."

Id.

106. At the same time, the final rule emphasizes that both the "enforcement discretion policies" and the phased-in approach are merely matters of prosecutorial discretion and that laboratories are legally required to comply with *all* medical-device regulations *immediately*. The rule states that "the phaseout policy does not in any way alter the fact that it is illegal to offer" laboratory-developed tests "without complying with applicable requirements" and stresses that "[r]egardless of the phaseout timeline and enforcement discretion policies … FDA retains discretion to pursue enforcement action for violations of the FD&C Act at any time, and intends to do so when appropriate." *Id.* at 37,295.

107. With respect to the "enforcement discretion policies," FDA further cautions that "[a]s with any enforcement discretion policy, FDA may update any of these policies as circumstances warrant or if the circumstances that inform these policies change." *Id.* at 37,297. FDA again emphasizes that "these enforcement discretion policies do not confer lawful marketing status on any [laboratory-developed tests] being marketed as described in the policies" and "do not in any way alter the fact that it is illegal to market [a laboratory-

developed test] that lacks required premarket authorization or is otherwise in violation" of federal law. *Id.*

108. The final rule also warns that FDA "intends to take action to enforce applicable requirements for [laboratory-developed tests] … as appropriate, taking into account any public health concerns as evaluated on a case-by-case basis." *Id.* For example, "if FDA receives reports, or otherwise learns of information, that raise safety or effectiveness concerns with [a laboratory-developed test] that falls within an enforcement discretion policy, FDA generally intends to take action with respect to requirements applicable to that specific [test]." *Id.*

109. Again and again throughout the final rule, FDA declares that no laboratory is safe from enforcement merely because its conduct is consistent with FDA's stated enforcement discretion policies. *See id.* at 37,301 ("[A]s noted elsewhere in this preamble, regardless of this or any other enforcement discretion policy, FDA retains discretion to pursue enforcement action at any time against violative [laboratory-developed tests] when appropriate."); *id.* at 37,304 (same); *id.* at 37,307 (same).

110. As to existing tests, the final rule also states that FDA will expect compliance with premarket review and quality system requirements whenever the test is "changed in certain, more significant ways that could affect its basic safety and effectiveness profile," such as "includ[ing] significantly different

technology" in the test. *Id.* at 37,305. FDA does not explain how a laboratory might determine when a difference in technology is so "significant" as to trigger an expectation of compliance.

111. Under the final rule, FDA thus continues to assert comprehensive authority to regulate virtually all laboratory-developed tests as medical devices. FDA then tries to mitigate the fallout from that regulatory sea change by announcing vague, non-binding enforcement discretion policies in a 150-plus-page preamble to its final rule. But FDA takes the position that even laboratories acting within the scope of those vaguely defined policies are violating federal law and that FDA can decide to prosecute them at any time, leaving laboratories "at the mercy of [FDA's] *noblesse oblige*.'" *FCC v. Fox Television Stations, Inc.*, 567 U.S. 239, 255 (2012) (quoting *United States v. Stevens*, 559 U.S. 460, 480 (2010)).

112. In response to comments questioning FDA's legal authority, FDA doubles down on its theory that professional laboratory testing services are medical "devices" just like pacemakers or test kits. "As an initial matter," FDA says, "FDA does not read the definition of device to encompass only physical objects." 89 Fed. Reg. at 37,331. And "[r]egardless" of that reading (*i.e.*, even assuming the "device" definition is limited to tangible products), FDA explains, "a test system" developed by a laboratory "is a physical product and a material thing" because it involves "a set of components—such as reagents,

instruments, and other articles—that function together to produce a test result." *Id.* In other words, FDA's position is that whenever laboratory professionals use multiple tangible articles together to perform a test, they are "manufacturing" a "device." While FDA superficially disclaims that view, stating that its "position is not that laboratory services are articles but that in vitro diagnostic products used in laboratories (such as test systems) are articles," FDA has effectively adopted a definition of "test systems" that conflates professional laboratory services with the articles used to perform those services.

113. Whereas the statutory definition of "device" refers to discrete objects or fixed assemblages of objects, which can typically be packaged and shipped, FDA's approach treats as a "device" even a set of transient relationships between physical articles used by a skilled professional. For example, under FDA's reductionist approach, if a surgeon uses multiple objects to perform a procedure, such as a scalpel and a set of sutures, the surgeon has "manufactured" a "device" by using those objects in combination.

114. In the final rule's preamble, FDA also asserts that the statutory term "article" cannot be limited to tangible goods because, in FDA's view, computer software can qualify as a medical device despite being "an intangible thing." 89 Fed. Reg. at 37,331–32. Even assuming FDA is correct that software may sometimes qualify as a device, that does not support FDA's assertion that

the "device" definition can be stretched to cover the intangible professional services provided by laboratory medical professionals, which are different from manufactured medical devices. As the Supreme Court has explained, while it is possible to conceive of "software in the abstract: the instructions themselves detached from any medium," "[w]hat retailers sell, and consumers buy," are "tangible," "physical cop[ies] of the software" that, whether "delivered by CD-ROM" or "downloaded from the Internet," are ultimately "contained in and continuously performed by" a piece of physical hardware such as a computer. *Microsoft Corp. v. AT&T Corp.*, 550 U.S. 437, 446–48, 449–51 (2007).

115. FDA acknowledges that the final rule will impose major burdens on laboratories, but as with the proposed rule, FDA underestimates the impact. FDA projects that the requirements in the final rule will initially affect about 79,114 existing tests offered by 1,181 existing laboratories, and that it will also affect about 10,013 new tests offered every year going forward. *See* FDA, Laboratory Developed Tests Final Rule: Final Regulatory Impact Analysis at 36, 54–55 (May 6, 2024) ("Final Impact Analysis") (attached as Ex. H). As FDA notes, "most facilities that will be affected by this rule are defined as small businesses and the final rule is likely to impose a substantial burden on the affected small entities." *Id.* at 6–7; 89 Fed. Reg. at 37,433.

116. Even under the generous assumption that FDA will adhere to its non-binding enforcement discretion policies, *see* Final Impact Analysis at 37–

38, FDA estimates that it will need to review an additional 103 premarket applications, 1,090 premarket notifications, and 267 de novo classification requests each year—a vast increase in each category compared to the average from 2017 to 2021, including more than a doubling of the number of premarket applications, *see id.* at 57.

117. FDA estimates that the compliance costs for laboratories will total well over $1 billion per year. *See id.* at 2, 135, 178. Over the next two decades, FDA projects that total costs associated with the final rule will range from $12.57 billion to $78.99 billion, with a primary estimate of $28.61 billion. *Id.* at 125.

118. FDA acknowledges that the huge "increased cost to laboratories" may cause price increases for customers and "reduce the amount of revenue a laboratory can invest in creating and/or modifying" tests. *Id.* at 127.

F. HealthTrackRX and other ACLA members face irreparable harm from FDA's final rule.

119. Under Fifth Circuit precedent, "the nonrecoverable costs of complying with a putatively invalid regulation typically constitute irreparable harm." *Rest. L. Ctr. v. U.S. Dep't of Lab.*, 66 F.4th 593, 597 (5th Cir. 2023) (collecting cases).

120. By FDA's own admission, the final rule will impose significant nonrecoverable compliance costs on regulated laboratories, including

HealthTrackRX and other ACLA members. *See* Final Impact Analysis at 125 (estimating compliance costs of about $101 million in year 1, $113 million in year 2, $386 million in year 3, and more than $1.6 billion every following year). These costs will be unrecoverable because FDA, like other federal agencies, enjoys sovereign immunity from monetary damages. *See Rest. L. Ctr.*, 66 F.4th at 598.

121. HealthTrackRX and other ACLA members will need to begin incurring these costs immediately. FDA has made clear that despite the "phaseout" timeline and "enforcement discretion" policies in the final rule, it "retains the authority to enforce any applicable requirements and pursue enforcement action *at any time*" against laboratories that offer laboratory-developed tests without complying with regulatory requirements applicable to medical devices. 89 Fed. Reg. at 37,372 (emphasis added). And even if FDA were to commit to not taking enforcement action before the dates set forth in the policy (and FDA has expressly disclaimed such a commitment), laboratories would still have to begin incurring compliance costs well in advance of those dates to ensure full compliance by the relevant deadline.

122. Although FDA greatly underestimates both the magnitude of unrecoverable compliance costs and how quickly laboratories will begin incurring those costs, even FDA suggests that laboratories' costs of compliance in the first year after publication of the final rule will range from $47.85 million

to $216.75 million, with a primary estimate of $101.46 million. *See* Final Impact Analysis at 125. Those unrecoverable costs alone are sufficient to establish that laboratories face irreparable harm from the final rule.

123. Moreover, FDA wrongly assumes that laboratories will be able to defer certain compliance costs for several years. For example, FDA predicts that costs associated with preparing and submitting premarket approval applications, premarket notifications, and de novo classification requests for laboratory-developed tests—costs that FDA acknowledges will easily run to billions of dollars—will not occur until the third year after publication of the final rule. *See id.* at 124–25.

124. Contrary to FDA's assumptions, laboratories cannot delay incurring these costs until just six to eighteen months before FDA says it will begin enforcing premarket review requirements. Indeed, to support premarket applications, laboratories will need to begin preparatory work immediately, including meeting with FDA reviewers to agree on analytical and clinical validation study protocols, running such validation studies, and otherwise compiling the voluminous material required to support FDA approval or clearance.

125. HealthTrackRx and other ACLA members have made substantial financial investments to maintain and expand their business—including opening new laboratories, acquiring assets, and hiring employees—in reliance

on the understanding that laboratory testing services are not subject to FDA regulation as medical devices and are instead regulated under CLIA and applicable state law. Dr. Reddy Decl. ¶ 24; Dr. Eisenberg Decl. ¶ 18; Dr. Fesko Decl. ¶ 16; Dr. Genzen Decl. ¶ 22; Dr. Morice Decl. ¶ 66.

126. FDA's final rule puts HealthTrackRx and other ACLA members in an untenable situation of regulatory uncertainty, which creates a serious risk of chilling investment in the maintenance of existing testing services and the development of new or modified testing services. Dr. Reddy Decl. ¶ 27; Dr. Eisenberg Decl. ¶ 17; Dr. Fesko Decl. ¶¶ 18–21; Dr. Genzen Decl. ¶¶ 47, 52; Dr. Morice Decl. ¶¶ 15–16, 58–65, 68.

127. ACLA members have already expended substantial time and capital to prepare for, and ensure that they are able to comply with, FDA's final rule. *See* Dr. Reddy Decl. ¶ 26.

128. If FDA's final rule is permitted to take effect, ACLA members will face even greater unrecoverable costs, often in the hundreds of thousands of dollars or more per test, in order to ensure that they can remain in compliance with federal law. *See id*. ¶ 29; Dr. Fesko Decl. ¶ 19; Dr. Genzen Decl. ¶¶ 50, 56.

129. If the final rule is allowed to remain in place, there is a substantial risk that some tests will no longer be available to help providers and patients because of the prohibitive costs of seeking FDA approval and clearance, especially for tests that are not high-volume. *See* Dr. Reddy Decl. ¶ 31; Dr.

Genzen Decl. ¶¶ 56, 58; Dr. Morice Decl. ¶¶ 16, 59–61.

130. Given the unrecoverable costs of complying with the FDA's medical device requirements, and the likelihood that device regulation will exacerbate an FDA-review bottleneck, the final rule will hinder innovation by making it more difficult for ACLA members to develop, and for patients to access, new and modified tests. *See* Dr. Reddy Decl. ¶¶ 32–37; Dr. Genzen Decl. ¶¶ 47–51; Dr. Morice Decl. ¶¶ 15–16, 59–65, 68; Dr. Fesko Decl. ¶ 21.

CLAIMS FOR RELIEF

COUNT 1
Violation of the Administrative Procedure Act—Contrary to Law, in Excess of Statutory Jurisdiction and Authority, and Contrary to Constitutional Right and Power
5 U.S.C. § 706(2)

131. Plaintiffs reallege and incorporate by reference each of the preceding paragraphs as if set forth fully herein.

132. Under the Administrative Procedure Act, a court must set aside agency action that is not in accordance with law or in excess of statutory authority. *See* 5 U.S.C. § 706. An agency action is invalid and must be vacated if it exceeds the power conferred upon the agency by the statute. *See Perez v. Mortg. Bankers Ass'n*, 575 U.S. 92, 104–05 (2015).

133. FDA's final rule is contrary to law and in excess of FDA's statutory jurisdiction and authority because it treats laboratory testing services as medical devices that are subject to regulation under the FDCA, when in fact

they are services performed by highly skilled healthcare professionals.

134. The text, structure, and history of the FDCA make clear that a device is a physical product, not a professional service. Treating laboratory testing services as devices would not only do violence to the statutory definition of "device," but would also require distorting numerous other statutory and regulatory provisions that confirm that FDA's device authority is limited to physical goods.

135. The text and history of CLIA provide further confirmation that laboratory services are not devices subject to regulation under the FDCA. In CLIA, Congress created a comprehensive framework for the regulation of professional laboratory testing services—including extensive personnel qualification requirements, quality controls, and proficiency testing—that is separate and distinct from the framework for regulation of manufactured medical devices under the FDCA. Congress first enacted CLIA in 1967, nine years before the Medical Device Amendments, and significantly expanded CLIA in 1988, twelve years after those Amendments. In doing so, Congress never so much as hinted at any existing authority of FDA to regulate laboratory testing services under the FDCA. And when Congress acted to create a distinct and uniform system of regulation for clinical laboratories, it clearly indicated that FDA had no such authority.

136. Although the clarity of the statutory text should put an end to the

inquiry, FDA's attempt to regulate laboratory testing services as devices also implicates the major questions doctrine. *See West Virginia*, 597 U.S. at 724. FDA's rule would mean that the entire clinical laboratory sector, which is a significant part of the U.S. healthcare system, has been breaking the law for nearly 50 years, and possibly much longer. And it would mean that going forward, the entire profession is operating unlawfully and can be subject to civil and criminal penalties at any time, with its only protection coming from a policy of enforcement discretion that FDA insists it is free to revoke at any time. The rule would also wreak havoc on clinical laboratories and the doctors and patients they serve, imposing billions of dollars in immediate, unnecessary costs and preventing countless new tests from ever being developed. And it would produce a vast increase in the number of medical-device applications FDA must review every year.

137. An agency cannot impose massive costs and place an entire profession under its thumb in this manner without, at minimum, a clear statement from Congress. The Supreme Court has repeatedly warned that agencies should not attempt, and courts should not abide, such drastic expansions of the agency's authority under a "'long-extant statute'"—especially where, as here, Congress has "conspicuously and repeatedly declined to enact" such an expansion itself. *West Virginia*, 597 U.S. at 724 (quoting *Util. Air Regul. Grp.*, 573 U.S. at 324).

COUNT 2
Violation of the Administrative Procedure Act—
Arbitrary and Capricious and an Abuse of Discretion
5 U.S.C. § 706(2)

138. Plaintiffs reallege and incorporate by reference each of the preceding paragraphs as if set forth fully herein.

139. Under the Administrative Procedure Act, a court must set aside agency action that is arbitrary and capricious, an abuse of discretion, or inconsistent with the requirements of reasoned decision-making. *See* 5 U.S.C. § 706. An action is arbitrary and capricious if agency acts outside the reasonable scope of its lawful authority, fails to articulate a satisfactory explanation for its actions, or fails to respond adequately and reasonably to comments and objections.

140. FDA has not acted consistent with the requirements of reasoned decision-making because it has not adequately responded to objections, provided a reasoned justification for its rule, or reasonably explained its sweeping assertion of new regulatory authority. FDA's decision to exercise enforcement discretion through the use of non-binding guidance in a preamble only underscores how unreasonable it is for FDA to outlaw an entire sector of professional services, especially given the reliance interests at stake.

141. Accordingly, even if Congress had granted FDA authority under the FDCA to regulate certain types of laboratory-developed tests as medical

devices, the agency has not exercised that authority consistent with the requirements of reasoned decision-making under the Administrative Procedure Act and the Constitution's separation of powers.

142. FDA's final rule cannot be allowed to stand because it is ultra vires, arbitrary and capricious, and an abuse of discretion.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs request that the Court:

A. Enter a declaratory judgment that FDA's final rule is contrary to law; in excess of statutory jurisdiction, authority, or limitations; and arbitrary or capricious, and that FDA is not authorized to regulate laboratory testing services as medical devices under the FDCA.

B. Enter an order that vacates FDA's final rule and enjoins FDA from enforcing the final rule and regulating laboratory testing services as medical devices under the FDCA.

C. Order such other and further relief as the Court deems just and proper.

Dated: May 29, 2024

Respectfully submitted,

/s/ Edward F. Fernandes

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EXHIBIT A

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 JAY REDDY, Ph.D.

I, Jay Reddy, Ph.D., declare as follows:

1. I am a resident of Denton, Texas. I am over the age of eighteen, and I am competent to provide this declaration.

2. I am the Senior Vice President of Laboratory and Clinical Strategy at HealthTrackRx. I have held that position for a little more than 2 years. I was previously the company's Vice President of Laboratory Operations.

3. I have worked at HealthTrackRx for more than 9 years.

4. I received my Ph.D. in Molecular Biology at Texas Women's University.

5. As a result of my professional experiences and background, I am familiar with the laboratory testing services and procedures that HealthTrackRx offers. I am also familiar with the legal and regulatory requirements that apply to laboratory-developed tests.

6. I am deeply concerned about the final rule issued by the Food and Drug Administration ("FDA") on May 6, 2024, and the enormous costs it will impose on clinical laboratories, such as HealthTrackRx. FDA's final rule also creates serious risks for patients by threatening to reduce their access to important and safe testing services.

HealthTrackRx

7. HealthTrackRx is one of the nation's premier infectious disease laboratories.

8. HealthTrackRx has its principal place of business in Denton, Texas.

9. For more than twenty years, HealthTrackRx has helped providers make informed clinical decisions by offering next-morning testing results to healthcare providers throughout the nation using accurate and targeted molecular diagnostic testing processes and procedures.

10. HealthTrackRx specializes in a particular type of testing service that employs a pathogen assay referred to as Real-Time Transcription Polymerase Chain Reaction ("RT-PCR"). The RT-PCR technology is used to detect bacteria and viruses on a molecular level. PCR testing services, which can be performed overnight, allow for faster and more accurate results than traditional culture assays, which can take 3 to 14 days (or even longer) to obtain results. By using advanced PCR testing, HealthTrackRx is able to help providers make better and more informed patient treatment decisions.

11. The company's testing services cover a wide variety of different specialties, such as otolaryngology and ophthalmology, and target viral, bacterial, and fungal pathogens that cause a range of everyday infections, including respiratory infections, urinary tract infections, genitourinary infections, gastrointestinal infections, wound infections, and onychomycosis.

12. All of HealthTrackRx's laboratories are certified by the United States Department of Health and Human Services under the federal Clinical Laboratory Improvement Amendments ("CLIA") to perform clinical tests on human specimens. All HealthTrackRx laboratories are enrolled in proficiency

testing programs run by the College of American Pathologists ("CAP") and the American Proficiency Institute ("API"), as well as an internal alternative proficiency testing assessment administered by the Quality Department. HealthTrackRx has a history of successful performance in all proficiency testing events, with extensive root cause analysis conducted in the event of any deviation from expected results.

13. All of HealthTrackRx's laboratories also participate in the rigorous accreditation program overseen by CAP, which is the "gold standard" accreditation program for molecular diagnostic laboratories.

14. HealthTrackRx has more than 300 employees and operates laboratories in Denton, Texas; Clarksville, Indiana; Marietta, Georgia; and Sherman Oaks, California. All testing personnel meet CLIA/CAP requirements, and HealthTrackRx employees in California are certified by the California Department of Public Health to perform testing. HealthTrackRx also employs professional "Certifying Scientists" to review quality control and raw data before releasing patient reports to providers. These professional scientists have a minimum of a Master's degree in a biological or chemical science, and most also have certification by the American Society of Clinical Pathology (MB (ASCP) or MLS (ASCP)).

15. The testing services provided by HealthTrackRx are carefully validated according to federal guidelines before those services are offered to

healthcare providers. Analytical and clinical performance evaluations are concluded before the launch of any new testing service, and tests are continuously re-evaluated throughout each year to ensure patient data integrity.

16. HealthTrackRx has assumed an active leadership role in educating the healthcare community about Antimicrobial Resistance, which is recognized by the Centers for Disease Control as one of the greatest threats to public health worldwide. Antimicrobial Resistance occurs when bacteria mutate over time and no longer respond to antibiotics, making infections more challenging to treat and increasing the risk of contagion, severe illness, and death.

17. HealthTrackRx helps providers by detecting antibiotic resistant genes and identifying pathogens that are difficult to culture. Because our best-in-class PCR tests meet demanding sensitivity and specificity standards, and because we are able to offer next-morning results that provide a personalized, patient-specific antibiotic summary, we are able to help providers identify appropriate antibiotics that work for their patients.

18. HealthTrackRx promotes antibiotic stewardship through active training on diagnostic stewardship. All new and existing accounts have ongoing training to help identify the appropriate tests for their patient

population. Appropriate test ordering is key to reducing unnecessary prescribing of antibiotics.

19. HealthTrackRx has an Advisory Board that is made up of leaders in the healthcare industry. Members of the Board include:

- **Barbara Alexander, M.D., FACP, FIDSA**, the company's Chief Medical Advisor and Chair of the Advisory Board. Dr. Alexander is a Professor of Medicine and Pathology at Duke University, where she serves as Director of the Transplant/Immunocompromised Infectious Diseases Services.
- **Josh M. Berlin, J.D.**, Chief Executive Officer of rule of three, LLC ("ro3").
- **Leah Binder**, President and Chief Executive Officer of Leapfrog Group.
- **Elizabeth Canis**, former Vice President for Emerging Business and Partnerships at Anthem.
- **Eric D. Hargan**, former Acting Secretary for the U.S. Department of Health and Human Services.
- **David B. Nash, M.D., MBA**, Founding Dean Emeritus at the Jefferson College of Population Health.

20. HealthTrackRx also has a Clinical Advisory Board, composed of leading experts in infectious disease and antimicrobial resistance. Our Clinical Advisory Board helps guide the company's development of new testing services and menus, seeking to improve patient outcomes and combat antimicrobial resistance. The members of our Clinical Advisory Board include:

- **Barbara Alexander, M.D., FACP, FIDSA**.

- **Cornelius J. Clancy, M.D.**, Director of the Mycology Program at the University of Pittsburgh, Associate Chief of the VA Pittsburgh Health System and Chief of Infectious Diseases, and a Member of the Infectious Diseases Society of America's Committee on Antimicrobial Resistance.

- **Barry Eisenstein, M.D.**, Chief Medical Officer and former Chair of the Scientific and Business Advisory Board of CARB-X.

- **Thomas M. File, Jr., M.D., MSC, MACP, FIDSA, FCCP**, Professor of Medicine and Chair of the Infectious Disease Section at Northeast Ohio Medical University.

- **Kimberly E. Hanson, M.D., MHS, FIDSA**, Professor of Medicine and Director of Transplant Infectious Diseases and Immunocompromised Host Service, and Section Head of Clinical Microbiology at the University of Utah.

- **Robin Patel, M.D.**, Elizabeth P. and Robert E. Allen Professor of Individualized Medicine, Professor of Microbiology and Medicine, Director of the Infectious Diseases Research Laboratory, and Co-Director of the Clinical Bacteriology Laboratory at the Mayo Clinic.

- **Adriana E. Rosato, SM (ASCP), MSC, Ph.D.**, Director of the Center for Molecular Medicine at the MaineHealth Institute for Research and Visiting Professor of Medicine at Tufts University.

The Consequences of FDA's Final Rule

21. In treating laboratory-developed tests the same as medical devices, FDA's final rule fundamentally misunderstands how laboratories, such as HealthTrackRx, perform professional testing services for the benefit of patients.

22. HealthTrackRx is not a manufacturer, and it does not manufacture products or articles of equipment. Its PCR testing services are not medical devices.

23. The molecular diagnostic services that HealthTrackRx's professionals perform at its laboratories at the request of healthcare providers involve medical procedures, protocols, and processes that are used to analyze at the molecular level tissue, blood, and other patient specimens as part of the practice of laboratory medicine.

24. HealthTrackRx has made substantial financial investments — opening new laboratories, hiring employees, developing additional testing services, and expanding its business — in reliance on the understanding that laboratory testing services are not subject to FDA regulation as medical devices and are instead carefully regulated under CLIA and applicable state regulatory regimes.

25. I am concerned about the substantial costs that FDA's final rule poses both for HealthTrackRx and for patients.

26. HealthTrackRx has already made substantial investments in order to prepare for, and ensure that it is able to comply with, FDA's final rule. Because there is no ready ability to recover money damages from FDA, it is unlikely that HealthTrackRx will ever be able to recover those investments.

27. If FDA's final rule is allowed to take effect, HealthTrackRx will face even greater unrecoverable costs and financial burdens in order to ensure that it is able to remain in compliance with federal law. Although FDA has announced carveouts that are supposed to reduce the consequences of FDA's decision to regulate laboratory-developed tests as medical devices, the carveouts create intolerable regulatory uncertainty, as FDA's rule states that the agency could change its mind at any time.

28. Notwithstanding the carveouts that FDA says it will observe as a matter of enforcement discretion, FDA's position appears to be that all laboratory developed tests are illegal under federal law —- and subject to civil and criminal penalties — unless they have been approved and cleared by FDA.

29. FDA's own estimates recognize that obtaining FDA approval and clearance could cost hundreds of thousands of dollars for each separate test — even if there is a predicate FDA-approved medical device that can be used as a reference product to compare to any specific test service for which a manufacturer seeks approval or clearance. If there is no predicate device, the costs are likely to be substantially larger, as professional laboratories will be required to make significant investments and undertake substantial efforts to demonstrate to FDA's satisfaction the safety and efficacy of tests.

30. FDA lacks the resources needed to oversee the prompt approval of potentially tens of thousands of laboratory-developed tests. I am therefore

concerned that when HealthTrackRx submits a test for FDA approval and clearance, the company will be forced to wait many months (if not longer) for approval or clearance. Any delay in providing approval or clearance could cause substantial harm by making it more difficult for HealthTrackRx to provide the essential testing services that healthcare providers rely on in order to make appropriate treatment decisions.

31. Moreover, there are tests that HealthTrackRx includes on its testing menu that, because they are not high-volume tests, may not justify the costs associated with seeking FDA approval and clearance. If FDA's final rule is allowed to remain in place, there are significant risks that some of these tests will no longer be available to help providers and patients.

32. FDA's final rule will create significant disincentives for financial investment by laboratories in new testing protocols and processes. The impact will be especially significant for specialized testing services.

33. For example, at the request of a group of expert ophthalmologists, HealthTrackRx worked to develop a cutting-edge PCR test that quickly diagnoses whether a corneal ulcer — also known as infectious keratitis — is caused by a virus, bacterium, or fungus. There is no FDA-approved device that ophthalmologists are able to use for this purpose. Infectious keratitis is a major cause of visual impairment and blindness, often affecting marginalized populations. Because the proper treatment of keratitis differs depending on

whether it is caused by a virus, bacterium, or fungus, quick and accurate diagnosis is important. With the right diagnosis, treatment can often cure the patient; a wrong diagnosis can often be debilitating. The PCR test that HealthTrackRx developed is critical because it allows providers to confirm quickly the source of a corneal ulcer and to identify appropriate treatment options.

34. Because this type of test is not used frequently or in large volumes, it is unlikely that it would ever have been developed if FDA's final rule were in place. Given the substantial costs of seeking FDA approval and clearance, no laboratory would invest the months of effort to develop and validate a new test for the benefit of patients with corneal ulcers.

35. As another example, HealthTrackRx has stepped up during the last two public health emergencies to help with the testing burden for both COVID-19 and Monkeypox. The Centers for Disease Control needed laboratory professionals to validate high throughput tests to help with the increased testing burden. Because the FDA-approved tests for both diseases were low throughput and could not meet testing demands, professional laboratories, including HealthTrackRx, were essential in providing services and addressing unmet needs that manufactured medical devices could not address. The FDA's final rule will stifle the very innovation that helped with testing demands in two public health emergencies in the last four years.

36. I am also concerned that FDA's final rule will prevent laboratories from innovating and customizing tests when necessary. One of the important features of laboratory-developed testing services is the ability of individual laboratories to modify their testing protocols and procedures to adapt to specific requests made by providers (and their patients). If FDA's final rule remains in place, however, I am concerned that the threat of FDA fines may discourage laboratories from customizing their professional testing services when needed by patients.

37. I have additional concerns that FDA's final rule will negatively impact both ordering providers and patients. HealthTrackRx has moved away from "static" panels to customizable menus. That approach allows the physician to request targeted testing based on the symptoms presented by the patient as opposed to relying on a "one size fits all" approach, which is how medical devices work. FDA's final rule could make customizable menus too expensive to pursue. That would force physicians to move back to relying on broad syndromic menus, which increase costs to patients. Increased costs reduce access to testing to those who cannot afford it, and in many cases, for those who need testing the most.

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

Executed on this 23rd day of May, 2024.

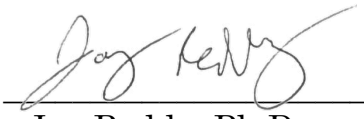
By: 
Jay Reddy, Ph.D.

EXHIBIT B

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 MARCIA EISENBERG, Ph.D.

I, Marcia Eisenberg, Ph.D., declare as follows:

1. I am a resident of Apex, North Carolina. I am over the age of eighteen, and I am competent to provide this declaration.

2. I have worked for Labcorp for more than 30 years, including in a variety of leadership positions. I am currently a Senior Vice President and the Enterprise Chief Scientific Officer at Labcorp.

3. I oversee research and development and science and technology for the company, which includes test development, optimization, and automation. I have been recognized and honored for my contributions to the advancement of forensic DNA testing, and I have been involved with the development and validation of hundreds of clinical assays used for patient care.

4. I earned a B.S. in biology, a B.A. in psychology, and an M.S. in molecular biology from the State University of New York at Albany. I earned a Ph.D. in molecular biology from the University of Kentucky.

5. My experience includes work with the National Institute of Environmental Health Sciences. I have been a member of the FBI's Technical Working Group on DNA Analysis Methods, and I was an appointed member of the National DNA Advisory Board during its lifespan.

Labcorp

6. Labcorp is a global life sciences and healthcare company. With nearly 100 laboratories in dozens of countries, Labcorp performs professional testing services for providers and patients across the world. Our services include doctor-requested testing, consumer-initiated testing, research and development laboratory testing, and clinical trial laboratory testing.

7. In 2019, Labcorp celebrated its 50th anniversary and the company's transformation from a local laboratory operating in a former hospital to a leading global life sciences company that is deeply integrated in guiding patient care.

8. Labcorp prides itself on leveraging cutting-edge science, technology, and innovations to find healthcare answers for patients. We pursue scientific advancements in clinical diagnostic testing and breakthrough treatments, relying on a professional team of more than 2,500 M.D.s and Ph.Ds.

9. Labcorp works to provide healthcare providers and patients with the highest quality and most comprehensive menu of testing services available. We have a growing list of more than 6,000 different routine and esoteric tests.

10. Our scientific experts and specialists focus on helping patients in areas of pressing need, including oncology, Alzheimer's, liver, and autoimmune diseases, as well as helping people prevent serious illness and remain healthy. The world-class diagnostic testing services that we provide help enable and accelerate patient care and access to innovative treatments, medicines, and new technologies that can change outcomes and lives.

11. The Labcorp Charitable Foundation, which was founded in 2020, has given out more than 341 grants to promote greater access to healthcare and education. These grants have focused on supporting food pantries and

summer meal programs for children, providing access to healthcare and patient support services for the underserved, broadening access to STEM education programming, and providing ongoing support for medical research, screenings, and programs that promote a healthy lifestyle.

12. Labcorp is constantly innovating and developing new testing services and updating older tests. In April and May 2024 alone, we developed numerous new LDTs, including for early Sjogren's Syndrome, Candida auris colonization screening, and others. We also updated dozens of other existing LDTs.

FDA's Final Rule

13. The new final rule issued by the Food & Drug Administration ("FDA") poses a significant threat to the nation's healthcare system and the longstanding practices and regulatory requirements that Labcorp has relied on to build and expand its business.

14. FDA is wrong to suggest that laboratory developed tests are equivalent to manufactured medical devices sold in interstate commerce. The professional testing services that laboratories provide are not instruments, machines, or physical objects that qualify as medical devices subject to FDA approval and clearance. Instead, they are an essential healthcare service that involves the exercise of professional medical expertise and judgment to provide clinical information to physicians and patients. Laboratory developed testing

services are an integral part of the broader practice of medicine. The professionals at Labcorp are expert technicians, M.D.s, and Ph.Ds; they are not manufacturers.

15. During my decades in the clinical laboratory industry, professional laboratory testing services have been regulated under the federal Clinical Laboratory Improvement Amendments Act of 1988 and by individual states under state law, not the FDA. Those regulations are designed to take account of the processes and procedures that are involved when professional clinicians engage in laboratory testing. In contrast, the requirements that apply to medical devices are a poor fit for regulating professional services. If the government wants to change the regulatory requirements that apply to clinical laboratories, that should be accomplished through legislation, not by re-tooling a statute that was never designed for that purpose.

16. The suggestion made by FDA in its final rule that Congress in 1976 somehow banned laboratory developed testing services unless and until they are approved and cleared by FDA would mean that thousands of laboratories have violated the law for more than half a century. That makes no sense.

17. It is also unfair. In its final rule, FDA has said that it does not intend to enforce the rules that apply to medical devices to existing laboratory developed tests, and it has suggested that it intends to limit when the agency will exercise its enforcement discretion against laboratories. But FDA has

made clear that it believes those testing services are subject to the medical-device requirements. FDA has suggested that it could change its mind about enforcement at any time. That creates an untenable situation of regulatory uncertainty.

18. Labcorp has made substantial investments to expand its professional testing capabilities in reliance on the existing regulatory system and the understanding that our large team of M.D.s and Ph.Ds provide professional testing services that are not subject to the same regulatory requirements as manufactured medical devices. Since the early 2000s, Labcorp has acquired assets and made substantial investments that have allowed the company to expand its testing capabilities and expertise in the following areas: (1) ultra-sensitive hepatis C testing, (2) molecular microbial testing, (3) anatomic pathology, (4) esoteric oncology, (5) genetic and oncology services, (6) forensics, (7) specialized toxicology, and (8) cardiovascular and metabolic disorders.

19. Under FDA's rule, for laboratories to avoid the risk of FDA changing its position and bringing future enforcement actions, they will need to seek FDA clearance or approval for the many tests that are already on the market and for every new testing protocol they might develop in the future. FDA does not have the personnel or financial resources necessary to review and approve all those testing protocols, which could take decades to complete.

Nor would it make sense for laboratories to undertake the cost and expense of seeking approval for all the different types of testing services they provide.

20. FDA's rule threatens either to force laboratories to provide services with an uncertain risk of future enforcement or to deprive patients of essential testing services. Neither option is in the interests of laboratories or the nation's healthcare system.

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

Executed on this 24th day of May, 2024.

By: Marcia Eisenberg
Marcia Eisenberg, Ph.D.

EXHIBIT C

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 YURI A. FESKO, M.D.

I, Yuri A. Fesko, M.D., declare as follows:

1. I am a resident of North Carolina. I am over the age of eighteen, and I am competent to provide this declaration.

2. I have worked for Quest Diagnostics ("Quest") for more than seven years. I currently serve as Quest's Chief Medical Officer.

3. I am a board-certified physician in the areas of oncology, hematology, and internal medicine. In my current role, I lead Quest's medical affairs organization and oversee the Company's medical team of approximately 700 MDs and PhDs. Prior to joining Quest, I was medical director of oncology for Duke Cancer Center of Wake County, where I was a member of the oncology faculty.

4. Because of my experience with Quest, I have a keen understanding of how laboratory testing services are developed and provided and of the meaningful differences between professional laboratory services and manufactured medical devices.

Quest Diagnostics

5. Quest is one of the world's leading providers of professional diagnostic testing services. It serves customers globally, and each year it provides testing services to approximately 1 in 3 adults and half the physicians and hospitals in the United States.

6. Quest's diagnostic testing portfolio is focused on three areas:

- General Diagnostics: Routine and non-routine testing and consultation services essential to healthcare delivery.
- Advanced Diagnostics: Genetic and advanced molecular testing and consultation services based on rich clinical, scientific, and medical expertise and innovation.

- Diagnostic Services. A wide range of capabilities that efficiently provide healthcare insights to individuals, employers, and institutions to support population health.

7. Quest is a leader in developing laboratory testing services, with clinical experts, resources, and other professional services all focused on helping to meet the needs of providers and patients. Its broad and deep menu of testing services includes 3,500 routine, esoteric, and genetic tests.

8. Quest maintains a nationwide network of clinical laboratories, including advanced laboratories as well as rapid response laboratories (smaller facilities where we can quickly perform an abbreviated menu of routine tests for customers who require rapid turnaround times). The company operates 24 hours a day, 365 days a year, with a nationwide network of patient service centers, phlebotomists in physician offices, and a range of connectivity resources, including call centers and mobile paramedics, nurses, and other health and wellness professionals.

9. Quest employs approximately 700 MDs and PhDs and approximately 23,000 phlebotomists, paramedics, nurses, and health and wellness professionals. It has a large in-house staff of medical and scientific experts, including medical directors, scientific directors, genetic counselors, and board-certified geneticists. These professionals provide medical and scientific consultation to healthcare providers and patients regarding the company's testing services, helping to improve health outcomes. The

company's professionals also publish original research in peer-reviewed publications, at medical and scientific conferences, and as a public service.

10. Quest is a leading provider of diagnostic information services for infectious disease, such as COVID-19 (including molecular diagnostic and serology antibody offerings), tuberculosis, and tick-borne disease. It also provides diagnostic solutions for emerging infectious diseases, such as Zika, West Nile Virus, SARS, and Influenza A H1N1. It has leading positions in drug monitoring and toxicology, in neurology diagnostics, in advanced cardiovascular diagnostic services, and in cancer diagnostics.

11. Quest is also a leading provider of workplace drug testing. It is certified by the U.S. Department of Health and Human Services to perform federally mandated drug testing using electronic custody and control forms for safety-sensitive workers. In addition, Quest is a leading provider of employer population health services, including biometric screenings, flu shots, and related preventative services that leverage clinical data to improve population health outcomes and reduce healthcare costs. The solutions provided by Quest enable employers to leverage screening insights to identify chronic disease risks, connect employees to needed in-network care, and empower better health.

12. As an organization dedicated to improving our patients' health, Quest aims to support a culture that is guided by "the 5Cs":

- Customers first: Every decision made by Quest Diagnostics starts with a patient or customer in mind. The quality of work is vital because the answers it delivers are a matter of life.

- Care: Quest is in the healthcare business, with care at the core of everything it does. Its professionals do the right thing with empathy, integrity, and respect to show each patient, customer, and colleague they matter.

- Collaboration: Creating a healthier world is a monumental task. The professionals at Quest work as a team, internally across departments and externally throughout the healthcare ecosystem and in the communities where its professionals work and live.

- Continuous improvement: Quest recognizes that delivering superior quality requires intention and innovation. It is committed to being better today than yesterday and even better tomorrow.

- Curiosity: The professionals at Quest are constant learners. To do their jobs, they must be relentlessly curious, because that is what it takes to move healthcare forward.

FDA's Final Rule

13. The final rule issued by the Food & Drug Administration ("FDA") on May 6, 2024, seeks to treat professional laboratory testing services as if they are manufactured medical devices and asserts sweeping authority to subject those professional services to the same regulatory requirements as medical devices under the Food, Drug and Cosmetic Act.

14. FDA's final rule is premised on the extraordinary view that in 1976, Congress prohibited the development and use of any laboratory tests that were not approved and cleared by FDA, and that in the ensuing five

decades, thousands of professional laboratory clinicians across the nation have been violating federal law by offering tests to physicians and patients without first seeking FDA approval and clearance. That makes no sense and is unfair to the thousands of Quest employees who are dedicated to helping patients by providing essential testing services.

15. FDA's final rule ignores the fundamental differences between professional laboratory testing services and manufactured medical devices. Quest is not a manufacturer. It is a healthcare organization dedicated to and focused on providing empathetic, high-quality, and individualized patient care. The professional diagnostic services that Quest provides are not physical objects or articles that qualify as medical devices. Instead, the information and consultation services that Quest provides require the exercise of medical expertise and professional judgment.

16. Quest has made substantial investments in reliance on the understanding that Congress has never granted FDA authority to treat professional diagnostic testing services the same as manufactured medical devices. Those services are instead regulated under a specialized, laboratory-specific framework set forth in the Clinical Laboratory Improvement Amendments of 1988 ("CLIA"). That framework was carefully designed and tailored by Congress to ensure the validity and appropriateness of the

processes and procedures that are followed when laboratory professionals develop and perform testing services.

17. Congress has recently considered legislation that would change the regulatory requirements for laboratory testing services. Congress has so far rejected calls to grant FDA authority to regulate laboratory developed testing services and has instead decided to keep the existing regulatory framework in place.

18. Even though Congress has never granted FDA authority to regulate laboratory professional services, FDA takes the position that all laboratory developed tests are subject to the statutory requirements that apply to manufactured medical devices (in addition to the laboratory-specific requirements that apply under CLIA). In an attempt to reduce some of the immediate negative consequences that this position would otherwise have on the nation's healthcare system, FDA has said that, at least for now, it does not intend to enforce certain regulatory requirements with respect to existing testing menus, and it has said that the agency will exercise its "enforcement discretion" not to enforce the statute in a variety of contexts. This attempt to soften the blow of its final rule does not solve the rule's many problems and only creates more regulatory uncertainty.

19. Most notably, FDA has emphasized that it could change its mind and end its supposed "enforcement discretion" at any time. That puts Quest

(and other laboratories) in an impossible position — either (1) expend substantial resources to go through FDA's costly approval and clearance process and have fewer resources available to invest in continued innovation and development, or (2) continue to provide the essential testing services relied on by one third of the nation's adult population and risk being subject to future enforcement action by FDA. No company should be put in that impossible position.

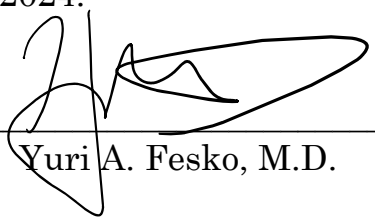
20. It is also unclear how the nation's laboratories are likely to respond to the uncertainty created by FDA's new rule. FDA's attempt to assert authority over an entire profession is a massive undertaking, and when laboratories start seeking FDA approval and clearance for their testing services the problems are only likely to increase. The costly requirements imposed by the medical device regulations are not calibrated to account for the professional and expert judgments made by laboratory professionals when developing and performing diagnostic testing services.

21. Moreover, FDA lacks the resources and experience to review and approve the many thousands of different laboratory tests that are available today and the many more tests that are likely to be developed in the future. It would take years (if not decades) for FDA to review, approve, and clear all of the laboratory tests that are offered by Quest and other laboratories. But no one knows how long FDA will continue to exercise enforcement discretion or

how it will respond if laboratories start seeking FDA approval and clearance. The risk of regulatory delay is significant, which could chill the incentives for laboratories to innovate and develop new testing processes and procedures needed to keep up with the pace of change in multiple medical specialties.

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

Executed on this 24th day of May, 2024.

By: 

Yuri A. Fesko, M.D.

EXHIBIT D

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.

EXHIBIT E

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 WILLIAM MORICE II, M.D., Ph.D.

I, William Morice II, M.D., Ph.D., declare as follows:

1. I am a resident of Rochester, Minnesota. I am over the age of eighteen, and I am competent to provide this declaration.

2. I have worked for Mayo Clinic for more than 24 years, including in a variety of leadership positions.

3. Since 2015, I have served as the President of Mayo Clinic Laboratories. Since 2023, I have served as the Chief Executive Officer and President of Mayo Collaborative Services, which includes Mayo Clinic Laboratories. Mayo Clinic Laboratories is Mayo Clinic's outreach reference laboratory service for external customers.

4. From 2015 to 2022, I served as the Chair of Mayo Clinic's Department of Laboratory Medicine and Pathology, Rochester, Minnesota, and I have long been affiliated with the Department's Division of Hematopathology, serving as a physician consultant on Mayo Clinic medical staff since 2000.

5. I am a Professor of Laboratory Medicine & Pathology at the Mayo Clinic College of Medicine.

6. I also serve on the College of American Pathologists, the leading accreditation organization for clinical laboratories under the program established by the Clinical Laboratory Improvement Amendments of 1988 ("CLIA").

7. Since 2017, I have served as a member of the Research and Innovation Board for the Brussels Academic Hospitals Laboratory, which is an international group of experts from different institutions dedicated to identifying areas of worldwide need for diagnostic services. I am also a founding member of the Bone Marrow Pathology Group, which is a group of

academic pathologists focused on clinical and laboratory research to identify and address diagnostic issues associated with bone cancer.

8. I earned my Bachelor of Science degree in biochemistry from Indiana University, Bloomington, as well as combined medical and doctoral degrees in biomedical sciences and immunology from the Mayo Clinic College of Medicine.

9. As a Mayo Clinic faculty member, my research has focused on the diagnoses of blood and bone marrow-derived cancers, including lymphoproliferative disorders of T cells and natural killer (NK) cells, plasma cells, and B cells. I have studied these disorders using a variety of methods, with a particular emphasis on flow cytometry, and with the aim to develop practical applications for clinical diagnosis.

10. I am a member of the Board of Directors of the American Clinical Laboratory Association ("ACLA"), and I am currently serving as the Board's Chair. ACLA is the national trade association representing leading laboratories that deliver essential diagnostic health information to patients and providers by advocating for policies that expand access to the highest quality clinical laboratory services, improve patient outcomes, and advance the next generation of personalized healthcare.

11. As a result of my professional experiences and leadership roles, I have significant knowledge of clinical diagnostic laboratory services. I engage

frequently with medical device manufacturers, including manufacturers of in vitro diagnostic ("IVD") test kits, and understand the substantial and meaningful differences between medical device products and laboratory-developed testing services. I am also familiar with the significant time and expense involved in seeking federal approval to market and sell medical devices to third parties.

12. I am generally familiar with the legal and regulatory requirements that have long applied to laboratory-developed tests, including the CLIA requirements that regulate the conduct of laboratories and the validation of laboratory diagnostic testing services. I am familiar with the state regulations for all states in which Mayo Clinic Laboratories does business. I am also familiar with the final rule issued by the Food and Drug Administration ("FDA") on May 6, 2024.

13. As described below, I am deeply concerned about FDA's final rule. FDA's position — that laboratory-developed tests are and have always been subject to all of the requirements of the federal Food, Drug, and Cosmetic Act, including premarket approval requirements for medical devices — is an implausible position that is contrary to decades of settled expectations in the healthcare profession.

14. FDA's final rule fails to appreciate that laboratory-developed tests are not manufactured products or devices; instead, they are services provided

by trained laboratory and medical professionals. When laboratorians develop a methodology to perform laboratory-developed testing services, they are no different from other health care professionals that develop protocols or methodologies for treating patients or diagnosing diseases.

15. FDA lacks the expertise to regulate the important professional healthcare services that clinical laboratories provide, and the radical change in regulation that the agency seeks to impose will stymie innovation and undermine laboratories' ability to help diagnose and treat diseases, especially those that are rare.

16. I am also deeply concerned that, because FDA lacks the resources to oversee the prompt approval of laboratory-developed tests, laboratories will face significant regulatory uncertainty and patients may be denied access to the essential medical services they depend on clinical laboratories to provide. In short, FDA's choice 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.

Mayo Clinic Laboratories

17. Mayo Clinic is the largest integrated, not-for-profit medical group practice in the world. It is committed to clinical practice, education, and research, and its experts work together to diagnose and treat the toughest

medical challenges and unmet needs of patients. It has more top rankings for high-quality patient care than any other healthcare organization.

18. Mayo Clinic's unwavering drive to create better medical care and its relentless pursuit of research helps patients by making earlier diagnoses possible and developing new cures. More than 1.3 million patients, from nearly 130 counties, visit Mayo Clinic campuses each year.

19. Mayo Clinic physicians are supported by the Department of Laboratory Medicine and Pathology, which performs testing services for diagnostic and therapeutic evaluations. More than 2,350 employees, working in numerous specialty laboratories, staff the Department. They form one of the largest clinical laboratories in the world, which performs more than 26 million tests annually. The laboratory's professional teams consist of highly experienced physicians, scientists, medical technologists, medical technicians, histotechnologists, cytology technologists, pathologist's assistants, phlebotomists, lab assistants, biologists, chemists, microbiologists, geneticists, genetic counselors, and other specialists.

20. Mayo Clinic's most extensive laboratory service facilities are located in Minnesota and are provided by more than 190 physicians and Ph.D. scientists. Besides serving Mayo Clinic patients, the laboratories also undertake testing for clinics and hospitals, both in the United States and in more than 50 countries worldwide.

21. Mayo Clinic's laboratory specialty areas include anatomic pathology, clinical biochemistry and immunology, clinical core laboratory services, clinical microbiology, community laboratory medicine and pathology, dermatopathology, experimental pathology and laboratory medicine, hematopathology, laboratory genetics, and transfusion medicine.

22. Mayo Clinic Laboratories is a reference laboratory that specializes in esoteric laboratory testing — testing for the most unusual, complex, and difficult cases. The laboratory was launched more than 50 years ago, in March 1971 and has always operated as a highly specialized laboratory housed within an academic medical center.

23. As part of providing medical diagnostic services to patients, Mayo Clinic Laboratories has always reflected Mayo Clinic's core mission — what are referred to as the "three shields": (1) integrated clinical practice, (2) research, and (3) education.

24. Mayo Clinic Laboratories has partnered since its inception with Mayo Clinic and its high-caliber faculty and state-of-the-art laboratories to help patients. For example, Mayo Clinic Laboratories has long provided second opinions on surgical pathology. When a pathologist or physician at another hospital, health system, or practice has a difficult diagnosis, they call Mayo Clinic Laboratories, which works with them and connects them to a physician or surgeon from Mayo Clinic to discuss the case. Research has also long been

a distinguishing mark of Mayo Clinic Laboratories, particularly in the context of developing new diagnostic tests and other groundbreaking medical services. In addition, Mayo Clinic Laboratories is well known for its educational programs offered to other healthcare providers on topics such as endocrine diseases, infectious diseases, surgical pathology, and liver pathology.

25. Fueled by the caliber of Mayo Clinic's academic medical faculty and its state-of-the art laboratories, Mayo Clinic Laboratories is an internationally respected laboratory that provides important and cutting-edge testing services to help diagnose and treat patients with some of the most complex conditions.

26. Mayo Clinic Laboratories currently serves more than 3,400 national and international clients and, in ordinary circumstances, performs approximately 35,000 testing services per day. Together with Mayo Clinic, Mayo Clinic Laboratories relentlessly innovates on behalf of patients, building the diagnostics ecosystem of the future to help physicians save and improve more lives.

Laboratory-Developed Testing Services

27. When a patient visits Mayo Clinic with a difficult or complex medical challenge, or when its physicians and scientists are asked to consult with physicians outside of Mayo Clinic, the patient's caregivers will turn to Mayo Clinic Laboratories and its expert laboratorians to help diagnose and

evaluate the patient. In these situations, existing or routine tests — including available FDA-cleared or approved tests may be incapable of providing the information required. Instead, Mayo Clinic physicians and scientists have to rely on combining medical expertise with research and diagnostic expertise to ensure that it can properly evaluate and analyze the patient's condition and then use that evaluation to diagnose the patient and develop effective treatment options.

28. Mayo Clinic Laboratories follows a rigorous process when developing new testing services. Laboratory teams focus on developing new tests when there is an unmet patient need and when it appears that new testing services could improve patient diagnosis, treatment, or care. Because the laboratory that develops a test must be knowledgeable about how the test will be used and understand the specimen type, range of detection, turnaround time requirements, and potential complementary tests, Mayo Clinic Laboratories has a large team of highly experienced physicians, scientists, medical technologists, medical technicians, histotechnologists, cytology technologists, pathologist's assistants, phlebotomists, lab assistants, biologists, chemists, microbiologists, geneticists, genetic counselors, and others.

29. When developing the necessary protocols and methodologies for a new test, interdisciplinary experts and specialists consult with other medical

experts, educators, and researchers at Mayo Clinic. Developing a new test requires a research and development process that documents standard operating procedures for each assay and includes basic analytical validation studies to show that assays satisfy clinical requirements. In addition, a variety of quality and process controls must be in place to verify that all steps of the assay are working appropriately, including extraction controls, controls to assess clinical accuracy, hybridization controls, external analyte controls, and/or internal controls for analytes expected to be presented in each test sample.

30. There are many examples of areas where Mayo Clinic Laboratories has developed groundbreaking approaches to providing the types of professional diagnostic services that are essential to helping patients. A few examples follow:

31. ***Cardiovascular testing.*** Mayo Clinic Laboratories has for more than two decades been at the forefront of cardiovascular genetic testing. The Laboratory's current test menu features 24 different panels that collectively include more than 300 genes linked to inherited cardiovascular disorders, many of which are rare and challenging to diagnose. Disorders can involve multiple genes and may present similarly to other disorders with distinct genetic causes.

32. When providing genetic specimen or similar testing services, Mayo Clinic Laboratories takes an expansive approach. A team of technicians, genetic counselors, Ph.D. geneticists, and physicians work together to analyze the genetic data and determine how the data correlates with the clinical picture of each individual patient. This correlation entails both review of each patient's family history and medical records and discussions with the treating clinicians.

33. There is significant professional medical expertise involved in developing well-thought-out gene panels to ensure that they are clinically useful and valid. In addition, professional expertise is required to interpret the results to ensure that the findings are accurate and consistent with the patient's overall clinical presentation. Mayo Clinic Laboratories' testing is part of Mayo Clinic's integrated clinical practice.

34. For example, I am aware of the services Mayo Clinic Laboratories provided to a Mayo Clinic patient who was under the care of a preventative cardiologist. The patient had both high cholesterol and stage 1 hypertension, but current risk calculators and traditional blood tests were not helpful in reaching an appropriate diagnosis because they did not take into account the patient's family history and because coronary artery disease and endothelial plaque formation are complex and multifactorial processes. As a result, the patient's treating cardiologist recommended to the patient that a sample be

sent to Mayo Clinic Laboratories for specialized ceramide testing. Ceramide testing uses liquid chromatography-mass spectrometry technology, which sorts through complex molecular compounds. By testing patients, the Laboratory is able to reveal more about heart disease and stroke risk than standard lipid tests, as ceramides are involved in plaque formation and can reflect inflammation, bad cholesterol, or coagulation and thickening of the blood. By evaluating the results of these tests, the treating physician was able to develop a tailored treatment plan for the patient that was appropriate to his risk level.

35. ***Cancer testing***. Another important area where Mayo Clinic Laboratories is a leader is in the area of cancer diagnosis and treatment, where laboratory testing services are relied on to provide crucial information to guide appropriate care in real time. Because cancer is such a complex disease about which our medical understanding continues to evolve, it is important to be able to account for emerging new medical information on discoveries and technological advancements.

36. Mayo Clinic has one of the most robust laboratory and pathology practices for cancer care in the world, offering testing services that span diagnostic, theranostic, and prognostic approaches. The comprehensive test menu at Mayo Clinic Laboratories includes numerous laboratory-developed tests that aid in providing both diagnostic and prognostic information and treatment selection guidance across the full spectrum of malignancies.

37. Mayo Clinic Laboratories has developed a suite of hematology and oncology, next-generation sequencing panels that are used to help diagnose patients depending on the genetic associations of an individual patient's cancer. Mayo Clinic Laboratories uses these panels to evaluate several gene mutations, rearrangements, and amplifications. The results of these analyses provide information that, along with correlation with the patient's clinical features, inform clinicians regarding the appropriate diagnosis and are used to guide treatment. This all helps to ensure that patients receive the best cancer care and are able to follow the best treatment strategies.

38. The laboratory-developed tests developed by Mayo Clinic Laboratories include those used to diagnose sarcoma, melanoma, lung, and colorectal cancers, including gastrointestinal stromal tumors. New panels have recently been developed to help evaluate patients for renal cell carcinoma, bladder and prostate cancer, gynecological cancer, endometrial cancer, and ovarian, fallopian tube, and peritoneal cancer. In addition, panels have been developed to test for B-cell lymphoma, chronic lymphocytic leukemia, T-cell lymphoma, plasma cell myeloma, and histocytic neoplasms.

39. These tests are not just a question of chemistry. They involve analyzing actionable genes that are carefully selected by a multi-disciplinary team of professional clinicians, geneticists, genetic counselors, and laboratory testing experts. The genes included on the testing panels are recognized as

clinically significant and are included in consensus group testing guidelines put forth by the World Health Organization, the National Comprehensive Cancer Network, the Intercultural Cancer Council, and European LeukemiaNet, among other governing bodies.

40. Because the experts who design the hematology panels are themselves hematopathologists, they are intimately familiar with the underlying disease. When questions arise, testing specialists collaborate with Mayo Clinic physicians to obtain their expert assistance with accurately interpreting the results. Moreover, each and every case is reviewed by a team of genetic experts, including technical experts, genetic counselors, and physician scientists, all of whom help to interpret the test results and ensure that they are accurate.

41. The interpretive report that accompanies the testing results describes in detail the gene variant detected and contextualizes the clinical significance from a diagnostic, prognostic, and/or therapeutic perspective. The report also may include information concerning relevant clinical trials. Even after the clinical report is provided to the treating physician(s), ongoing consultation between the laboratory professionals and the treatment team is common.

42. I was personally involved in developing standards for classifying and identifying different types of leukemia and, in particular, T cell, large

granular, lymphocytic leukemia and NK-cell, large granular, lymphocytic leukemia, which are rare blood cancers of cytotoxic effector lymphocytes. Diagnosis involves evaluating blood and bone marrow samples for clonal abnormal T- and NK-cells through a variety of methods, all of which are synthesized by the pathologist and correlated with the clinical features to render the correct diagnosis.

43. Early diagnosis of this rare disease is often crucial for appropriate management and optimizing the outcomes for patients. That is especially true because patients with T cell and NK cell disorders often present with symptoms that are similar to other diseases and other types of leukemia. Early detection can ensure that the disease is properly treated and allow patients to live long and fulfilling lives.

44. The standards I helped develop to support the practice of medicine in this important area of pathology are reported in guidelines published by the World Health Organization and are part of the standard of care for classification of patients with this rare disease. *See* Rita Alaggio, et al., The 5th Edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022 Jul;36(7) 1720-1748. doi: 10.1038/s41375-022-01620-2. Epub 2022 Jun 22. Erratum in: Leukemia. 2023 Sep;37(9):1944-1951. PMID: 35732829; PMCID: PMC9214472.

45. As this publication recognizes, evidence-based classification of disease is fundamental for the treatment of individual patients, monitoring global disease incidence, and investigating all aspects of disease causation, prevention, and therapy.

46. ***Infectious diseases***. Mayo Clinic Laboratories is also internationally renowned for offering a broad selection of laboratory-developed tests designed for the rapid identification and in-depth characterization of the causative agents of infectious diseases. The Laboratory has developed culture techniques, immunoassays, antimicrobial susceptibility testing, and molecular methods for rapid detection, identification, and characterization, as well as providing treatment guidance for microbial pathogens.

47. For example, Mayo Clinic Laboratories has developed a test that assists with identifying nervous system infections. The assay uses shotgun metagenomic sequencing to apply complex bioinformatic analysis to all DNA and RNA sequences in a cerebrospinal fluid specimen. The sequences deriving from humans are removed, and the remaining sequences are then analyzed by expert technicians for a potentially pathogenic microorganism.

The Material Differences Between Laboratory-Developed Testing Services and FDA-Approved Medical Devices

48. Laboratory-developed testing services are materially different from the types of instruments, machines, or physical objects that qualify as and are properly considered to be medical devices.

49. Laboratory-developed testing services are essential professional healthcare services that are provided in connection with the practice of medicine. The types of tests developed by federally-certified CLIA laboratories reflect unique assays that yield important clinical information about a patient that can be used by physicians and other medical professionals to inform and guide that patient's care and treatment.

50. When Mayo Clinic Laboratories develops and performs laboratory-developed testing services, it is not acting as a device manufacturer. Mayo Clinic Laboratories are managed by professional physicians and scientists with expert knowledge regarding the clinical implications of each test result and how those results can impact patient care. The type of interaction and collaboration between a clinical laboratory and the care team that I describe above is completely at odds with the idea of a laboratory as a device manufacturer. Medical device manufacturers do not perform patient care using their medical devices; medical device manufacturers do not collaborate

with treating physicians; medical device manufacturers are not considered part of the care team for a patient.

51. By subjecting laboratories to regulation as device manufacturers, FDA's final rule will significantly undermine the relationship between laboratory professionals and the care teams that rely on the diagnostic services of clinical laboratories.

52. Performing a test in a CLIA-certified laboratory involves (1) collecting and appropriately preparing a tissue, blood, or other patient specimen that is sent to the laboratory for testing and analysis; (2) conducting an analysis of the sample by using reagents, instrumentation and other equipment to evaluate the specimen quantitatively and/or qualitatively; and (3) preparing a report that reflects the results of the analysis, the expert medical judgment used in conducting the analysis, and patient-specific information that is shared with a physician or team of physicians to assist in patient diagnosis and treatment.

53. FDA-approved medical devices, including reagents, instrumentation, microscopes, spectrometers, and other sophisticated types of medical equipment, are routinely used by laboratory technicians when providing diagnostic testing services. Medical devices are appropriately subject to FDA's clearance and pre-approval oversight because they are

instruments, machines, or other physical objects that are packaged, labeled, and produced by manufacturers to be used and sold to third parties.

54. Unlike medical devices, laboratory testing services are not a type of equipment, machine, or physical object. They instead reflect medical protocols, information, procedures, and techniques that are used by healthcare professionals to evaluate and diagnose patients. Whereas medical devices are typically sold to healthcare providers or patients for their own use, laboratory-developed tests are not sold or shipped to third-party purchasers. Instead, these testing services are performed by the laboratory itself, and the material to be tested — human blood, tissue, or other specimen samples — is sent to the laboratory for its expert medical analysis. Professional laboratory-developed testing services are performed by expert laboratory technicians in consultation with medical experts and are integral to the broader practice of medicine.

55. To provide a simple analogy: When a patient visits his doctor, the doctor may use certain devices to perform medical procedures. The doctor might, for example, use a biopsy needle to obtain a tissue sample for subsequent analysis. The biopsy needle is an FDA-regulated medical device and must be cleared or approved by FDA before it can be obtained and used by the doctor. In contrast, the technique the doctor follows in performing the biopsy procedure and the information she deems relevant to evaluating her patient — for example, deciding where to place the needle to avoid sensitive

tissue and whether or how to use anesthetics or ultrasound guidance — is a healthcare service that is provided to the patient by a trained professional in connection with the traditional practice of medicine. The fact that the biopsy procedure uses a device does not transform the procedure itself into a medical device.

56. The same is true for professional laboratory-developed testing services. The equipment, machines, and other instruments used to analyze a blood, tissue, or other sample from a patient are medical devices — like an ultrasound or biopsy needle — that must be approved or cleared by FDA and qualified and validated for use by the laboratory pursuant to the requirements of CLIA. But the sophisticated protocols that laboratories develop and use to test and evaluate the samples received from patients are not themselves instruments, machines, or pieces of equipment.

57. Laboratory-developed testing services have long been subject to regulation under CLIA, a specific statutory and regulatory framework tailored for clinical laboratories. In addition, several states have their own requirements relating to laboratory testing services and the practice of medicine. Most significantly, New York has developed an extensive set of diagnostic-specific, risk-based requirements that apply to laboratory-developed tests offered to New York state residents.

58. One key aspect of the existing regulatory requirements is the flexibility provided to the professionals at clinical laboratories to develop new testing protocols and modify existing ones for the purpose of diagnosing and guiding innovative treatment for patients. When individual patients present unexpected or unusual challenges, laboratory-developed tests are used in combination and may be modified to address the patient's specific circumstances, which can lead to discovering new diagnostic approaches and new testing protocols.

59. I am deeply concerned about the consequences of FDA's new rule for patients and for the ability of Mayo Clinic physician specialists to treat patients effectively. The most significant consequence of FDA's rule will be to make it more difficult for patients to continue to obtain the essential testing services they need. Seeking FDA clearance and approval for medical devices is very expensive and time-consuming. According to FDA, laboratories will face enforcement action if they fail to obtain such clearance or approval for most new testing services and most significant modifications of existing testing services. And even where FDA says it will exercise enforcement discretion (such as for some existing services), the agency insists it can change that policy at any time.

60. If FDA's final rule is allowed to take effect, clinical laboratories that want to protect themselves — and not rely on FDA's open-ended exercise

of enforcement discretion — will need to seek FDA clearance or approval for the tens of thousands of tests that are already on the market and for every new testing protocol they might develop in the future. That is unrealistic. Many laboratory-developed tests are low-volume tests that are used infrequently. These types of tests do not generate sufficient revenue to justify going through the very expensive FDA clearance or approval process.

61. Moreover, FDA lacks the personnel and financial resources necessary to efficiently review all of the testing services provided by professional laboratories and grant the necessary clearances and approvals. On average, it takes FDA months — and sometimes years — to clear or approve a new medical device. There are tens of thousands of different types of tests provided by laboratories across the United States, and there is no practical way for FDA to review, approve, and clear all of them.

62. It is also unclear how FDA intends to apply its new rule to modifications that are made to existing tests, which are critical to improving laboratory-developed tests and ensuring that they reflect the latest scientific advances. Under existing law, when FDA approves a medical device, the device must be manufactured to the approved specifications, and modifications to the device may need to be separately approved by FDA. As noted above, making modifications to existing testing protocols for particular patients is an essential part of the diagnostic testing process. Clinical laboratories, such as

Mayo Clinic Laboratories, frequently make adjustments to tests to respond to the specific circumstances of individual patients or to incorporate new biomarkers to reflect the latest scientific advances. Preventing laboratories from making these modifications without first going through the time-consuming and expensive FDA clearance or approval process would harm both patient care and innovation.

63. The consequences of not having laboratory-developed testing services available would be particularly devastating to the quality of care for patients suffering from rare diseases, many of whom come to Mayo Clinic. One of the particular advantages of laboratory-developed tests is the ability to determine — through a process of elimination — whether a patient has biomarkers for a particular disease.

64. To the uninitiated, it may seem to be only a minor consequence if certain tests are not developed, as only a small number of patients may suffer from any particular rare disease. But that misunderstands how tests are used. Tests are often most useful not for determining that a patient has or may have a particular disease ("ruling in" that disease), but for determining what diseases the patient does *not* have ("ruling out" diseases). Furthermore, tests developed within the laboratory in response to clinical need often provide new insights into previously identified diseases. Through the implementation of laboratory-developed tests, patients with more or less aggressive forms of a

disease are often identified, significantly impacting both their care and the psycho-social response to their diagnosis.

65. Eliminating diseases is often the best way to design an appropriate treatment regimen for a patient, even if no existing test is available to determine precisely what disease the patient does have. As a result, even tests that are used to diagnose especially rare diseases are an extremely valuable tool when diagnosing patients with unknown conditions.

66. Mayo Clinic has invested substantial resources into research and medical care — and into Mayo Clinic Laboratories — in reliance on the existing regulatory regime and on the understanding that Congress has never granted FDA authority to regulate professional laboratory testing services. These settled expectations would be undermined if FDA is permitted, for the first time ever, to take control over all the services provided by clinical laboratories by treating those services as equivalent to medical devices.

67. On several occasions, Congress has evaluated legislation that would change the regulatory requirements for laboratory testing services. But Congress has not enacted legislation and has instead declined to empower FDA with authority to regulate laboratory-developed tests. For many of us who are aware of those legislative debates, FDA's new rule appears to be an attempt to circumvent the political process and exercise sweeping authority that has never been granted to the agency by Congress.

68. In any event, as a practical matter, Mayo Clinic Laboratories will have less money to invest in developing new and innovative testing services if its resources have to be dedicated to obtaining FDA clearance or approval. Moving resources away from helping patients and in the direction of 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.

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

Executed on this 28th day of May, 2024.

By: _____
William Morice II, M.D., Ph.D.

EXHIBIT F

DEPARTMENT OF HEALTH & HUMAN SERVICES Office of the Secretary

The General Counsel
Washington, D.C. 20201

Privileged & Confidential
Attorney Client Communication
Pre-Decisional

MEMORANDUM

TO: Stephen Hahn, M.D., Commissioner of Food and Drugs

CC: Eric D. Hargan, Deputy Secretary
Brian Harrison, Chief of Staff
Stacy Amin, Deputy General Counsel & Chief Counsel
Anand Shah, M.D., Deputy Commissioner of Food and Drugs
Keagan Lenihan, Chief of Staff FDA
Danielle Steele, Counselor to the Secretary

FROM: Robert Charrow, General Counsel

SUBJECT: Federal Authority to Regulate Laboratory Developed Tests

DATE: June 22, 2020

Introduction

We have been asked by departmental leadership to review the legal bases—both substantive and procedural—for FDA's regulation of laboratory developed tests ("LDT").[1] This memorandum summarizes the results of our analyses.

Since 1992, FDA has taken the position in draft guidances, manuals, and web postings that LDTs are devices within the meaning of the Food, Drug, and Cosmetic Act ("FDCA" or "Act") § 201(h) and subject to the Agency's jurisdiction. Most recently, FDA announced on its website that

> FDA generally has not enforced premarket review and other legal requirements [with respect to LDTs]. However, LDTs for which an HHS [Emergency Use Authorization] declaration justifies a need (and that potentially meet the EUA criteria) present a higher risk. This is because they are developed to diagnose serious or life-threatening diseases or conditions that not only have serious implications for individual patient care, but also for analyses of disease progression and public health decision-making. Thus, FDA requests that developers of such LDTs submit information about their tests to help FDA better understand their design, validation, and performance characteristics.

[1] "A laboratory developed test (LDT) is a type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory." https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests (Sept. 27, 2018).

https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/information-laboratories-implementing-ivd-tests-under-eua (March 1, 2020) (last viewed June 15, 2020). We understand that some stakeholders, including many state university laboratories, have complained that this policy hindered their ability to develop and use LDTs to detect the virus that causes COVID-19.

We have undertaken a review of the relevant legal authorities and regulatory processes so as to advise departmental leadership, FDA, and other policymakers of FDA's authority in this area, especially in light of COVID-19. Specifically this memorandum addresses: (i) whether an LDT is a medical device; (ii) if so, under what circumstances, if any, does FDA have the jurisdiction to regulate LDTs; and (iii) whether FDA can properly regulate in this area without notice and comment rulemaking. We also discuss a potential re-assessment of relevant delegations in light of the foregoing analysis.

Summary of Conclusions

We believe that the Medical Device Amendments of 1976 ("MDA"), Pub. L. No. 94-295, may be broad enough, in certain settings, to accommodate FDA's view that LDTs, as opposed to the procedures used to run those tests, are "devices," within the meaning of section 201(h) of the FDCA.[2] However, the Agency's jurisdiction to regulate these devices is not uniform and not as plenary as it is for a traditional device; this lack of jurisdictional uniformity is dictated by the FDCA itself. FDA relies on FDCA section 301(k) and the premarket review regime in sections 510(k) and 515 as the primary means of exercising authority over LDTs. This theory has several potential weaknesses. First, it appears likely that LDTs, even if they satisfy the constitutional and statutory "interstate commerce" requirements of the FDCA, would likely not satisfy the separate "commercial distribution" requirement of the premarket review provisions at sections 510(k) and 515. Section 301(k), the primary provision dealing with prohibited acts, turns on whether the device is "held for sale." While courts in the past have given that term a broad reading to include devices that never leave a physician's office, a plain meaning assessment may not be as agency-friendly. Second, many first-line sophisticated laboratories are operated by state public health departments or academic medical centers at large state universities. These laboratories, by definition, are not "persons," within the meaning of the Act, and not subject to many of the Act's requirements, including registration (§ 510(c)), premarket review (§§ 510(k), 515), and adverse event reporting (21 C.F.R. pt. 803).

Third, the process that FDA used to ordain that LDTs are devices subject to the usual breadth and depth of FDA regulation is, in my view, inconsistent with the rulemaking provisions of the Administrative Procedure Act ("APA"), 5 U.S.C. § 553. Although the FDCA does not mention laboratory tests, FDA's various issuances have sought to fill this gap. However, where that gap-filling binds the Agency and has significant legal, regulatory and financial implications for those outside of the Agency, it is a legislative rule. This is especially the case, here, where as recently as last year, FDA has taken quasi-enforcement action on the basis of its determination that an LDT is a device, and where the FDA determination is inconsistent with the Secretary's existing regulations. The APA requires that legislative rules be issued through notice and

[2] Given that FDA has not expressed its view in a rule subject to notice and comment rulemaking, its determination that an LTD is a medical device would not enjoy *Chevron* deference, but rather lesser *Skidmore* deference.

comment rulemaking coupled with a Regulatory Flexibility Act ("RFA") analysis. *See* 5 U.S.C. § 601 *et seq*. Here, FDA did neither.[3]

All of this is not to say that during a national public health emergency, FDA would lack authority to seize or take other appropriate action against fraudulent or dangerous LDTs. Its authority, though, would not derive from the FDCA. Under the Public Health Service Act § 361(a), 42 U.S.C. § 264(a), the Public Health Service agencies, including FDA and CDC, have authority "to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession." FDA has used this authority to enjoin facilities that transplant stem cells and it could be used in those rare cases when an LDT poses undue risk. There may also be other federal agencies with authority to take action in such circumstances.

Background

When the MDA amended the FDCA, Congress authorized the then-Secretary of Health, Education, and Welfare to regulate medical devices through, among other things, premarket review—notification and approval—and the imposition of sanctions on those that failed to heed FDA's regulations or orders. The MDA broadly defined "device" to include, among other things, an "in vitro reagent . . . intended for use in the diagnosis of disease." MDA § 3(a)(1)(A). Laboratory developed tests—tests developed in a single clinical laboratory and used exclusively in that laboratory—were never mentioned in the MDA, in the House Report accompanying it, or during the floor debates.

In 1988, though, Congress addressed clinical laboratory testing when it enacted CLIA, codified at 42 U.S.C. § 263a, which among other things, instructed the Secretary of Health and Human Services to "issue standards to assure consistent performance by laboratories issued a certificate under this section of valid and reliable laboratory examinations and other procedures." 42 U.S.C. § 263a(f)(1). CLIA also required the Secretary to conduct inspections of laboratories to ensure compliance with established standards. *See* 42 U.S.C. § 263a(g). Since CLIA certification is a prerequisite to receiving Medicare payment, it was viewed primarily as Spending Clause legislation and delegated to CMS for enforcement. Thereafter, the Secretary issued comprehensive rules governing clinical laboratories. *See* 42 C.F.R. pt. 493. With respect to laboratory developed tests, those regulations provide as follows:

> Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as textbook procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable:
>
> (i) Accuracy.
> (ii) Precision.
> (iii) Analytical sensitivity.

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[3] 21st Century Cures: Examining the Regulation of Laboratory Developed Tests, Before the H. Comm. on Energy and Commerce Health Subcomm. 113 Cong. 91 (2014) (preliminary transcript) ("21st Century Cures hearing") (statement of Dr. Jeffrey Shuren, Director, CDRH. FDA); *see also id.* at 68.

(iv) Analytical specificity to include interfering substances.
(v) Reportable range of test results for the test system.
(vi) Reference intervals (normal values).
(vii) Any other performance characteristic

42 C.F.R. § 493.1253(b)(2) (2019) (emphasis added). To perform LDTs, laboratories have to be certified under CLIA to perform highly complex tests. *See id.* § 493.17(c)(4). These tests can usually only be performed under the supervision of a board certified pathologist. *See id.* § 493.1443(b)(3) (noting that some with Ph.Ds may be grandfathered and medical doctors may satisfy the certification requirement in other ways). CLIA appeared to have occupied the field for regulating LDTs.[4]

FDA seems to have first suggested that LDTs are subject to its jurisdiction in a 1992 draft compliance policy guide aimed at regulating products sold to laboratories for research use only. The draft compliance guide stated that "laboratories have been manufacturing 'home brew' products, either from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes" and asserted that "[t]hese products are subject to the same regulatory requirements as any unapproved medical device." FDA, *Draft Compliance Policy Guide: Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation* at 4 (Aug. 1992).

In 1997, FDA issued a final rule regulating analyte specific reagents ("ASR"), the type frequently sold to commercial laboratories. In the preamble to the final ASR rule, FDA expressly stated that LDTs were devices subject to FDA jurisdiction: "FDA believes that clinical laboratories that develop [LDTs] are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act."[5] 62 Fed. Reg. 62,243, 62,249 (col. b) (Nov. 21, 1997).

During the intervening seventeen years, FDA did little to regulate LDTs, although it did issue a draft guidance for certain high-risk LDTs known as "in vitro diagnostic multivariate index assays" in 2007.[6] Things changed, though, in 2014, when FDA issued two draft

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[4] Pursuant to a delegation of authority from the Secretary of HHS, FDA is delegated limited authority under CLIA, to "implement CLIA's complexity categorization provisions as they apply to *commercially available tests* . . ." https://www.govinfo.gov/content/pkg/FR-2004-04-27/pdf/04-9527.pdf (emphasis added). This authority pertains to categorizing the complexity of such tests for purposes of CLIA. As discussed below, this involves physical test kits that are "commercially available" in interstate commerce, and not the type of laboratory developed testing at issue in this memorandum. This delegation of authority was recognized in statutory language in section 3057 of the 21st Century Cures Act. The Centers for Disease Control and Prevention (CDC) also provides analysis, research, and technical assistance with respect to CLIA and manages the Clinical Laboratory Improvement Advisory Committee (CLIAC).

[5] Statements in preamble which are not mirrored in the text of the rule are treated as interpretive rules, at best. *See Wyeth v. Levine*, 555 U.S. 555 (2009).

[6] See: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-diagnostic-multivariate-index-assays-draft-guidance-industry-clinical-laboratories-and-fda . In addition, in 2010, FDA held a widely-attended public meeting to solicit feedback from stakeholders on LDTs.

guidances.[7] Not only did the Agency continue to assert its authority under the FDCA to regulate LDTs, but it noted that, as part of that authority, it was going to require registration for all LDTs, to classify LDTs under section 513, and to require premarket notification or approval under sections 510(k) or 515, respectively, for certain LDTs.

The draft guidances' legal justification for treating LDTs as devices subject to FDA jurisdiction relied on the FDCA definitions of "device" and "manufacturer." A "device" under FDCA § 201(h) is defined as:

> an instrument, apparatus, implement, machine, contrivance, implant, *in vitro reagent*, or other similar or related article, including any component, part, or accessory, which is—(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. (emphasis added)

A "manufacturer" is defined as any person who owns or operates any establishment engaged in the "manufacture, preparation, propagation, compounding, assembly, or processing of a device" is required to register that establishment with FDA. FDCA § 510(b), (c).[8] Under FDA's logic, because an LDT is system using one or more *in vitro* reagents, and hence a "device," that is assembled or prepared in the clinical laboratory, and hence "manufactured," it is, in the Agency's view, subject to its regulatory jurisdiction. Most of the draft guidance is a lengthy justification as to why regulation is warranted and how that regulation would be implemented.

FDA received more than 50 comments in response to the draft guidances. Some were supportive, but many questioned the Agency's legal authority, questioned the absence of any documentation to support its claim that LDTs posed a risk, and questioned whether agency action of this magnitude could be undertaken without going through notice and comment rulemaking. On November 18, 2016, following the Presidential election, FDA announced that it would not finalize the two guidance documents. Notwithstanding this decision, FDA's position—announced initially in a compliance policy guide, later in a preamble to a regulation, and most recently in the web posting—that LDTs are medical devices within its jurisdiction remains in place. At issue is whether that decision is legally viable.

Analysis

I. Many LDTs Are Likely Medical Devices, But Even Those That Are May Fall Outside of FDA's Full Regulatory Regime

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[7] *See FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)* (Oct. 3, 2014) and *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* (Oct. 3, 2014).

[8] The regulation would not reach state public health laboratories or state university laboratories, since they are not "persons" within the meaning of the law. *See* FDCA § 201(e).

FDA maintains that LDTs are systems that include *in vitro* reagents intended to diagnose disease in humans and therefore are medical devices subject to FDA jurisdiction. Those opposing this position argue that LDTs are not physical embodiments, *e.g.*, "contraptions," but rather are processes or services, and therefore not devices. FDA is correct that, by definition, *in vitro* reagents are devices, but that does not necessarily lead to the conclusion that LDTs fall within FDA's jurisdiction. For purposes of this memorandum, we assume that had FDA made that determination through notice and comment rulemaking, it would be entitled to *Chevron* deference and would likely withstand scrutiny under that standard. However, even assuming that LDTs are medical devices, three additional requirements must be satisfied before FDA can implement its most significant regulatory authorities: (i) the "device" must satisfy the constitutional and statutory "interstate commerce" requirements; (ii) the device itself must be in commercial distribution or held for sale; and (iii) the laboratory must be a "person." We believe that the first requirement may be easy to establish with respect to certain authorities; the second more difficult to establish; and the third one cannot be established, as a matter of law, in many significant instances.

A. Statutory Interstate Commerce Requirement

The Constitution grants Congress power "[t]o regulate commerce with foreign nations, and among the several States, and with the Indian tribes." U.S. Const., art. I, § 8, cl. 3. Since the 1940s, the Supreme Court has construed the Commerce Clause broadly. *See, e.g.*, *Wickard v. Filburn*, 317 U.S. 111 (1942). In addition to regulating the channels of interstate commerce, and persons and things therein, Congress has authority to regulate activities that "substantially affect" interstate commerce. *Nat'l Fed'n of Indep. Bus. v. Sebelius*, 132 S. Ct. 2566, 2578 (2012). The Court's current constitutional interpretation provides Congress wide berth to regulate local, noncommercial activities that have only a nominal or indirect connection to interstate commerce. *See, e.g.*, *Gonzales v. Raich*, 545 U.S. 1, 22 (2005); *Katzenbach v. McClung*, 379 U.S. 294, 300-01 (1964); *United States v. Wrightwood Dairy Co.*, 315 U.S. 110, 121 (1942); *Wickard*, 317 U.S. at 128-29;. Given the breadth of the Court's interpretation, the Commerce Clause poses no barrier to FDA's theory of jurisdiction.

In the years since *Wickard*, Congress also expanded FDA's statutory jurisdiction to cover some intrastate activities. Congress revised the FDCA in 1948 to clarify that its prohibitions against adulteration and misbranding apply to articles that are held for sale within a state after being shipped in interstate commerce.[9] Amendments in 1976 authorized FDA to seize misbranded or adulterated medical devices without proof that they have traveled in interstate commerce. *See* FDCA § 304(a)(2). FDA also has authority under the Public Health Service Act ("PHSA") to prohibit false labeling of biological products whether or not they move in interstate commerce, and section 361 of the PHSA authorizes FDA regulation to prevent the spread of communicable disease without any interstate commerce limitations. However, despite

[9] As enacted in 1938, section 304(a) of the FDCA authorized the seizure of articles that were adulterated or misbranded "when introduced into or when in interstate commerce." 52 Stat. 1040, 1044. In 1946, the Ninth Circuit Court of Appeals held that this provision did not empower the government to seize adulterated pasta that was sitting in a warehouse after traveling in interstate commerce. *United States v. Phelps Dodge Mercantile Co.*, 157 F.2d 453 (9th Cir. 1946). In response, Congress amended section 304(a) in 1948 to also permit the seizure of an article that is adulterated or misbranded "while held for sale (whether or not the first sale) after shipment in interstate commerce." *See also* FDCA § 301(k) (prohibiting any act that results in an article being adulterated or misbranded "if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce").

these extensions of FDA jurisdiction, the Agency still lacks statutory authority to regulate a large segment of wholly intrastate conduct. Nonetheless, as those regulated by FDA have generally engaged in interstate commerce in some fashion, courts have tended to make statements regarding FDA's statutory jurisdiction as broad as the Commerce Clause, and the Agency prevails in the overwhelming majority of cases where its jurisdiction is challenged because a component of the drug or device was transmitted in interstate commerce. We offer below, in case a litigant were to assert that their conduct is wholly intrastate, advice regarding how FDA can successfully assert that its regulation of LDTs satisfies the statutory interstate commerce requirement in section 301(k) and otherwise consider its litigation position or review its regulations in light thereof.

1. Section 301(k)

Section 301(k) of the FDCA (21 U.S.C. § 331(k)) prohibits:

> The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded. (emphasis added).

The ability of the Agency to satisfy the statutory interstate commerce requirement in section 301(k)[10] hinges on whether a laboratory can show that everything used in its tests came from within the state.[11] In *United States v. Regenerative Sciences, LLC*, 878 F.Supp.2d 248 (D.D.C. 2012), *aff'd*, 741 F.3d 1314, 1326 (D.C. Cir. 2014),[12] two Colorado physicians developed a cellular therapy for orthopedic patients that involved harvesting stem cells from a patient's bone marrow or synovial fluid, culturing those cells for several weeks in a laboratory with growth factors from the patient's blood, placing the cultured cells into a syringe along with the antibiotic doxycycline and other additives, and injecting the contents of the syringe into the patient's injured area. The doctors formed Regenerative Sciences LLC ("Regenerative") to commercialize this practice. FDA officials inspected Regenerative's facilities in 2009 and 2010 and found that its laboratory operations did not conform to FDA manufacturing regulations. When FDA charged Regenerative with manufacturing and distributing adulterated and misbranded biological drug products in violation of section 301(k) of the FDCA and section 351(k) of the PHSA, the defendant physicians responded that they were lawfully practicing medicine within the state of Colorado and that their procedure fell outside FDA's regulatory purview.

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[10] We believe that section 301(k) is the FDA's most viable avenue for regulating LDTs. The Agency would face an uphill challenge if it used the adulteration and misbranding provisions at FDCA sections 301(a) or 301(b). The former requires the "introduction . . . into interstate commerce . . . . of the device" while the latter requires the "adulteration or misbranding . . . of any . . . device . . . in interstate commerce." Since the LDT never leaves the laboratory, it would be difficult for FDA to establish a violation of either subsection.

[11] The Act presumes, through a rebuttable presumption, that the Agency has jurisdiction. *See* FDCA § 709.

[12] Our discussion of *Regenerative Sciences* borrows from an outstanding article by Dr. Anna Laakmann. *See* Anna Laakmann, *Customized Medicine and the Limits of Federal Regulatory Power*, 19 VAND. J. ENT. & TECH. L. 285 (2016).

The district court focused on whether defendants' actions were directly connected to interstate commerce. FDCA section 301(k) prohibits any act "with respect to, a . . . drug . . . if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded." The court held that the manipulated cellular brew was "held for sale," a fact not contested by defendants. The court further went on to hold that

> [d]efendants do not dispute that the doxycycline is shipped from out of state to their facilities in Colorado. *Id.* Therefore, because a component of the drug in this case is shipped through interstate commerce prior to its administration to the patient, the "interstate commerce" requirement [of section 301(k)] is also met.

878 F.Supp.2d at 259.

The defendants' conduct satisfied the statutory interstate commerce requirement only because the doxycycline was shipped into Colorado from out of state and added to the stem cells prior to the mixture's administration to patients. Had the doxycycline been manufactured in Colorado and shipped intrastate, FDA would have lacked a jurisdictional hook. Alternatively, suppose the defendants had administered the doxycycline separately rather than mixing it with the stem cells in a single syringe. If the procedure were modified to comprise two separate injections—a first syringe of stem cells and a second syringe of doxycycline—FDA presumably would lose its regulatory authority under the FDCA, even if the doxycycline were shipped from out of state. In this case, the defendants would be prescribing doxycycline for off-label use, an activity that FDA lacks power to regulate regardless of its connection to interstate commerce. It was the mixing of the doxycycline, an approved drug, with other material that created FDA's jurisdictional hook.

Thus, under the terms of *U.S. v. Regenerative Sciences, LLC*, in order for FDA to satisfy the statutory interstate commerce requirement in section 301(k), at least one element of an LDT must come from outside the state.[13] With the exception of some academic medical centers, most laboratories use LDTs that have at least one component that came from out-of-state, so we believe FDA can usually successfully defend its jurisdiction in this regard.

2. Section 510(k)

Premarket review, which is set out in section 510(k), was central to the 2014 guidances and is the primary difference between regulation under CLIA and regulation under the FDCA. FDCA section 510(k) (21 U.S.C. § 360(k)) provides:

> Each person who is required to register under this section and who proposes to begin *the introduction or delivery for introduction into interstate commerce* for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, report to the Secretary . . . action taken by such person to comply with requirements under section 514 [related to performance standards] or 515 [related to premarket approval] which are applicable to the device. (emphasis added).

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13 The Act presumes, through a rebuttable presumption, that the Agency has jurisdiction. *See* FDCA § 709.

Section 510(k) has a meaningful grammatical difference from section 301(k). Section 301(k) prohibits the sale in interstate commerce of a component or other aspect of a device that is then altered or manipulated. Hence, if a laboratory were to purchase in interstate commerce any of its reagents, which it then modified or used to modify other reagents, it would satisfy the jurisdictional prerequisite in section 301(k). However, under section 510(k), the premarket review requirements are only triggered when one proposes to introduce or deliver the device into interstate commerce, even if the reagents were purchased from another state. The typical LDT, though, never physically leaves the laboratory. There is no "introduction" and no "delivery."

Thus, while the actions of the laboratory operator may have been sufficient to support regulation under the Commerce Clause, as having a substantial effect on interstate commerce, those actions may not be sufficient, if challenged by a savvy litigant, to satisfy the statutory requirements of section 510(k) or section 515 (premarket approval), which uses identical language.

B. "Held for Sale" or "Commercial Distribution" Requirement

1. Section 301(k)

Section 301(k) only applies if an article is "held for sale . . . after shipment." Courts have tended to interpret section 301(k)'s "held for sale" requirement very broadly—far broader than the plain meaning of the statutory text. But it is unclear whether the current Supreme Court would ignore the plain meaning of the text and affirm these expansive readings.

Case law supports the assertion that the "held for sale" standard of section 301(k) has long been afforded a liberal reading, encompassing "[a]ll articles, compound or single, not intended for consumption by the producer." *United States v. Cassaro, Inc.*, 443 F.2d 153, 156 (1st Cir. 1971)(citing *Hipolite Egg Company v. United States*, 220 U.S. 45, 54 (1911)). The Supreme Court has explained that that 301(k)'s "held for sale" requirement is "designed . . . to extend the [FDCA's] coverage to every article that had gone through interstate commerce until it finally reached the ultimate consumer." *United States v. Sullivan*, 332 U.S. 689, 697 (1948). The United States government has repeatedly advocated for this expansive reading of "held for sale," and stated that the requirement is satisfied if the product can be shown to have been used for any purpose other than personal consumption. *See, e.g., United States v. Rhody Dairy, L.L.C.*, 812 F.Supp.2d 1239 (E.D. Wash. 2011); *United States v. Scenic Dairy, L.L.C.*, 2011 WL 3879490 at *14 (W.D. Mich. Sep. 1, 2011); *United States v. Torigian Labs., Inc.*, 577 F. Supp. 1514, 1521 (E.D.N.Y. 1984); *Articles of Animal Drug Containing Diethylstilbestrol,* 528 F. Supp. 202, 205 (D. Neb. 1981); *United States v. Articles of Device (Acuflex; Pro–Med),* 426 F. Supp. 366, 368 n.3 (W.D. Penn. 1977).

Several courts have held that the phrase "held for sale" extends to physicians using devices in the treatment of patients. *See, e.g., United States v. Kaplan,* 836 F.3d 1199, 1208 (9th Cir. 2016). In *Kaplan*, the Ninth Circuit held that a doctor's use of a device (in that case, single-use plastic needle guides used during prostate biopsy exams) in the course of treating a patient is considered a "sale" within the meaning of "held for sale" in section 301(k). 836 F.3d at 1208. This makes sense—the single-use medical device is being consumed (i.e., sold) when used by the doctor, because the doctor is using the item with the patient during the course of a service. In contrast, LDTs usually involve the development of technologies and processes to conduct

testing activities. For example, Medicare does not pay for the physical embodiment of any LDT or any other laboratory test. LDTs are more analogous to a doctor who creates and develops a replicable procedure, rather than a doctor who uses a medical device during an ordinary course of treatment. Just as the doctor's development and use of a medical procedure would not be considered to be "held for sale," the development and use of LDTs would also not be considered "held for sale" under the common meaning of that term.

In short, even though courts have given a liberal reading to the "held for sale" requirement, it is unclear whether that reading is sufficient to support liability under section 301(k) with respect to LDTs. Even in light of this uncertainty, we assume for purposes of our analysis that courts would adopt a liberal reading and apply that section to LDTs such that FDA could defend its current position.

2. Sections 510(k), 513(f), and 515

Similar to section 301(k)'s "held for sale" requirement, section 510(k) requires that persons subject to it "begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device . . . ." Similar language is used in section 513(f) and 515(b). There do not appear to be any judicial interpretations of "commercial distribution" as used in these classification and premarket review sections. But this phrase is used in the grandfathering provision of the FDCA, and with respect to that provision, FDA has interpreted "commercial distribution" to mean "on the market" or "actively promoted" for a specific purpose. *See, e.g., United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, 994 (W.D. Mich. 1985); *see also Northwest Tissue Center v. Shalala*, 1 F.3d 522, 535 (7th Cir. 1993).

The plain meaning of this phrase makes it much narrower than section 301(k)'s "held for sale" requirement. First, the term "commercial" relates to "commerce" which means the "buying or selling of commodities on a large scale involving transportation from place to place." WEBSTER'S NEW COLLEGIATE DICTIONARY 223-24 (1980). Second, the term "distribution" means to "supply." *Id.* at 330. This means that if LDTs are to satisfy the "commercial distribution" standard, they must be viewed as goods or commodities that are sold and dispersed beyond the laboratory. This, of course, does not occur. Each LDT remains *in situ*, and is not treated as merchandise by the Secretary for payment purposes, but rather as a service. For example, under Medicare part B, the Secretary only pays for clinical laboratory services. *See* Social Security Act § 1861(s) (defining "medical and other health services" as including diagnostic laboratory tests); § 1834A (referring to the information generated by laboratory tests). Thus, the Secretary does not purchase the physical embodiment of any LDT or any other laboratory test, for that matter.

The FDA definition of "commercial distribution" appears to be to be in keeping with the phrase's plain meaning, namely, "any distribution of a device intended for human use which is held or offered for sale but does not include . . . "[i]nternal or interplant transfer of a device between establishments within the same parent, subsidiary, and/or affiliate company." 21 C.F.R. § 807.3. The development and use of LDTs involves purely internal transfers of LDTs because payors or clinicians are not paying for the LDT itself. Thus, even if LDTs could be viewed as being "held for sale," they certainly almost always involve only internal transfers, or no transfers at all, and thus would not, if challenged by a savvy litigant, satisfy the plain meaning

of FDA's regulation.

To marginalize the importance of movement outside the walls of the laboratory is to equate "held for sale" and "commercial distribution," which would be inconsistent with both its plain meaning and the well-established canon of statutory interpretation that the use of different words or terms within a statute demonstrates that Congress intended to convey a different meaning for those words. *See Russello v. United States*, 464 U.S. 16, 23 (1983); *Persinger v. Islamic Republic of Iran*, 729 F.2d 835, 843 (D.C. Cir. 1984) ("When Congress uses explicit language in one part of a statute to cover a particular situation and then uses different language in another part of the same statute, a strong inference arises that the two provisions do not mean the same thing."); *Nat'l Insulation Transp. Comm. v. ICC*, 683 F.2d 533, 537 (D.C. Cir. 1982); *Russell v. Law Enforcement Assistance Admin.*, 637 F.2d 354, 356 (5th Cir. 1981) (stating the "well settled rule of statutory construction that where different language is used in the same connection in different parts of a statute it is presumed that the Legislature intended a different meaning and effect") (internal quotation marks omitted); *NLRB v. Food Fair Stores, Inc.*, 307 F.2d 3, 10 (3rd Cir. 1962) (stating the rule of statutory construction which holds that different words appearing in the same statute are presumed to have different meanings). Even words with remarkably similar definitions can still convey a unique or distinct meaning or flavor from words that are similar or even synonymous in nature because of their differing tone or usage within a sentence.

C. The "Person" Requirement—Sections 510(c), 510(k), 515(c), and 21 C.F.R. pt. 803

In addition to the statutory commerce clause, the "held for sale," and the "commercial distribution" requirements of the FDCA, portions of the Act only apply to a "person." Thus, the registration and premarket review requirements of section 510(c) and 510(k), premarket application requirement of section 515(c),[14] and the adverse event reporting requirements of 21 C.F.R. pt. 803 apply only to "persons." *See* 21 C.F.R. § 803.3(1) (stating that a "*Manufacturer* means any person"). Under the Act, though, a "state" is not "person."

1. State is Not a "Person"

Many of the more sophisticated laboratories that are the ones most likely to first develop LDTs in response to an infectious disease are located in state public health departments and academic medical centers at state universities. A state, including its departments and state-owned universities, is presumed by definition not to be a "person." *See Vt. Agency for Nat. Res. v. U.S. ex rel. Stevens*, 529 U.S. 765 (2000) (applying its "longstanding interpretive presumption that 'person' does not include the sovereign" to find that a state is not a "person" within the meaning of the False Claims Act).[15] That presumption is not necessary here because the Act defines "person" to "include[] [an] individual, partnership, corporation, and association."

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[14] The term "person" is defined in the Agency's premarket application rules as including "any individual, partnership, corporation, association, scientific or academic establishment, Government agency, or organizational unit thereof, or any other legal entity." 21 C.F.R. § 814.2. Inasmuch as the regulation is inconsistent with the definition of "person" in the Act, as including governmental entities, we believe that definition is invalid.

[15] Counties and local governmental entities are "persons" under the FDCA. *See, e.g., Cook County, Ill. v. U.S. ex rel. Chandler*, 538 U.S. 119 (2003) (holding that a county is a "person" under the False Claims Act).

FDCA § 201(e). The Act separately defines "State," "except as used in the last sentence of section 372(a) of this title, [to] mean[] any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico." *Id.* § 201(a). The two definitions are not linked or cross-referenced. Thus, a "person" is not a "State."

2. Premarket Review, Registration, and Related Provisions Only Apply to "Persons" and Not States

Section 510(c) requires "[e]very person upon first engaging in manufacture . . . of . . . a device . . . shall register with the Secretary . . . ." The premarket notification provision of section 510(k) applies to "[e]ach person who is required to register under this section . . . ." Inasmuch as a state would not be required to register, it is also not required to file a premarket notification under section 510(k). If a device manufacturer does not take advantage of this pathway, it is generally subject to review under other the more rigorous premarket review pathways in the Act, such as the premarket approval in section 515 or the *de novo* review in section 513(f)(2). For most manufacturers, this is true by operation of two provisions in the statute. First, under section 513(f)(1) of the FDCA, a non-grandfathered device is automatically classified in class III unless the device "is substantially equivalent to another device" or has been classified pursuant to a petition or request, such as a *de novo* request. If such a device cannot be found to be substantially equivalent under the 510(k) pathway and if it has not been classified through another process, such as the *de novo* process, it is automatically classified in class III. Second, under section 515(a)(2), a device that is in class III by virtue of section 513(f) is "required to have ... an approval under this section of an application for premarket approval." Devices that are subject to these provisions and that lack premarket approval are adulterated. *See* FDCA § 501(f)(1)(B).

In the case of a state actor, though, the normal interplay between sections 501, 510, 513, and 515 breaks down. First, a state is not required to file a premarket notification under section 510(k) or to register under section 510(c). Second, to avoid being automatically treated as a class III device, section 513(f) merely requires that the device is "substantial[ly] equivalen[t]" to another lawfully marketed device. The section does not require that the Secretary make this finding or receive a report under section 510(k). Even assuming that section 513(f) applied and the device were by default classified into class III, that would still not impose any burdens on a state because it is likely that the premarket approval provision of section 515 does not apply to states and may not apply to LDTs, at all, and the adulteration provision also does not apply to states.

A device is adulterated if it were classified under section 513(f) into class III; a class III device, under section 515(a) "is required to have an approval under this section of an application for premarket approval . . . ." This presupposes that the state actor is required to file such an application. Section 515(c), though, limits those who may file applications to "persons:" "[a]ny person may file with the Secretary an application for premarket approval for a class III device." FDCA § 515(c)(1) (emphasis added). It would be anomalous to require an approved application from an entity not required to file an application. One could argue that the phrase "any person may file" does not foreclose a state from filing a PMA. Courts, though, have viewed similar or identical phrases in other statutes as restricting the class that can file. Thus, under the False Claims Act, "[a] person may bring a civil action for a violation of section 3729

for the person and for the United States Government." 31 U.S.C. § 3730(b). No one has suggested, following the Court's decision in *ex rel. Stevens*, that a state could act as a relator and file a qui tam suit under section 3730(b). We believe the most natural way to read these provisions is recognize that when the FDCA and MDA were enacted and amended no one contemplated that they would apply to states. This is especially so given that the penalty provisions of the FDCA only apply to "persons." *See* FDCA § 303. The fact that state public health and academic medical center laboratories appear to fall between the regulatory cracks in the case of LDTs, strongly suggests that the Act was never intended to reach these services.

As a result, FDA's registration, premarket review, and adverse event reporting requirements would not, if challenged by a sophisticated litigant, likely apply, as a matter of law, to any state-owned laboratory, whether in a state department of public health or university.

In sum, although it appears that FDA was acting within its discretion by treating LDTs as medical devices and that section 301(k) could be applied, its premarket review authority would not apply to LDTs, because the provisions require the device itself (*i.e.*, the reagent) to be placed into commercial distribution. Further, the registration, premarket review and adverse event reporting requirements only apply to "persons." State laboratories are unlikely to be considered persons within the meaning of the FDCA.

II. FDA's Policy that LDTs Are Devices Was Adopted Without Notice and Comment Rulemaking or a Regulatory Flexibility Analysis and Is Therefore Void

The APA establishes the procedures federal administrative agencies must use for "rule making," defined as the process of "formulating, amending, or repealing a rule."[16] 5 U.S.C. § 551(5). "Rule," in turn, is defined broadly to include "statement[s] of general or particular applicability and future effect" that are designed to "implement, interpret, or prescribe law or policy." *Id.* § 551(4); *see Perez v. Mortgage Bankers Ass'n*, 575 U.S. 92, 95–96 (2015). Rules fall into two broad categories—legislative rules and interpretive rules. Legislative rules can only be issued through notice and comment rulemaking, formal rulemaking or negotiated rulemaking; interpretive rules can be issued unilaterally. *See* 5 U.S.C. § 553(b). Therefore, whether an agency's issuance is a legislative rule or interpretive rule can have major consequences. Differentiating between the two, though, is complicated.

We believe that FDA's determination that an LDT is a device is a legislative rule for at least three independent reasons: (1) it fills a gap in the Act; (2) the Agency has treated its determination as legally binding forming the basis of enforcement and the exercise of enforcement discretion; and (3) the Agency's determination is inconsistent with an extant legislative rule of the Department.

A. FDA's Guidances and Determinations Are "Gap Filling" and Therefore Legislative Rules

First, a legislative rule "performs a legislative function when it makes 'reasonable but arbitrary (not in the "arbitrary and capricious" sense) rules that are consistent with the statute or regulation under which the rules are promulgated but not derived from it, because they represent

16 A stricter standard applies to Medicare under Social Security Act § 1871, where policy statements that affect substantive rights are subject to notice and comment, even if they would not qualify as legislative rules.

an arbitrary choice among methods of implementation.'" *Catholic Health Initiatives v. Sebelius*, 617 F.3d 490, 495 (D.C. Cir. 2010) (citing *Hoctor v. USDA*, 82 F.3d 165, 170 (7th Cir. 1996)). Gap-filling is a quintessential characteristic of a legislative rule.

FDA's determination starting in 1992, confirmed in 1997, reconfirmed in the 2014 draft guidances, and reconfirmed in its January 13, 2017 White Paper that LDTs are devices were all gap-filling policy determinations with significant economic and regulatory implications. The proposed LDT framework in the 2014 draft guidances would have required FDA to review virtually all LDTs. Under the White Paper, FDA review would be limited to "new and significantly modified high and moderate risk LDTs." White Paper at 4–5. As a result, FDA envisions that the process could be completed in four years, rather than the rather prolonged nine-year period originally envisioned in the draft guidances. In the White Paper, the Agency also stated that "[t]o protect patients from tests that could lead to harm, the Agency would retain its ability to enforce premarket review, quality systems, and other applicable requirements for any LDT, including those listed above, if the agency identified one or more of the following, taking into account all available evidence." *Id.* at 4. It also represents a clear choice, opting to define an LDT as a device; it thereby filled a gap in the statute, a quintessential characteristic of a legislative rule.

Nor is this a case where one can argue that the organic legislation unmistakably leads to the conclusion that LDTs are devices and an enforcement action can be based solely on the statute. Laboratory developed tests are not mentioned in the FDCA nor are they defined in it. Rather, they are only defined in FDA guidances and similar issuances. *See, e.g.*, *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* at 5 (Oct. 3, 2014) (defining LDT) ("Guidance Document"). It would be difficult to argue that FDA regulation of LDTs is so inherent in the FDCA that no regulation is necessary. This is especially so where the Secretary has issued rules implementing Medicare and CLIA that strongly suggest that LDTs are not devices and not within FDA's jurisdiction.

The argument that LDTs could be regulated without a regulation is also belied by the public comments submitted in response to the 2014 draft guidances which challenged FDA's contention that an LDT is a device. One commenter argued that

> [i]t is far-fetched to suppose that laboratory-developed testing services become medical devices in their own right merely because they sometimes utilize other medical devices. FDA's own regulations recognize the distinction between a service that uses devices and a device itself. For example, the FDA regulation excluding laboratories from device registration requirements specifically recognizes that laboratories' "primary responsibility to the ultimate consumer is to … provide a service through the use of a previously manufactured device." 21 C.F.R. §807.65(i) (emphasis added). Laboratories may well draw on both reagents and laboratory equipment of many kinds in executing their clinical testing services, but that plainly does not render the services these laboratories perform themselves "medical devices."

Comment submitted by Paul D. Clement & Laurence H. Tribe on Behalf of the American Clinical Laboratory Association at 9.

FDA's ability to regulate LDTs is not inherent in the language of the Act, which is silent

on the point. When, as here, the statute is silent, an agency's attempt to describe the contours of its authority is "gap-filling." Gap-filling, though, can only occur through notice and comment rulemaking. *See Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 843–44 (1984).

B. FDA's Determinations Were Intended to Be Binding and Have the Force and Effect of Law

Second, an agency action that purports to impose legally binding obligations or prohibitions on regulated parties—and that would be the basis for an enforcement action for violations of those obligations or requirements—is a legislative rule. An agency action that sets forth legally binding requirements for a private party to obtain a permit or license is a legislative rule." *National Min. Ass'n v. McCarthy*, 758 F.3d 243, 251–52 (D.C. Cir. 2014); *see also Appalachian Power Co. v. E.P.A.*, 208 F.3d 1015, 1021 (D.C. Cir. 2000). Correspondingly, legislative rules, as opposed to interpretive rules, "'grant rights, impose obligations, or produce other significant effects on private interests;' 'narrowly constrict the discretion of agency officials by largely determining the issue addressed;' and '[has] substantive legal effect.'" *U.S. Telecom Ass'n v. FCC*, 400 F.3d 29, 35 (D.C. Cir. 2005) (quoting *Batterton v. Marshall*, 648 F.2d 694, 701–02 (D.C. Cir. 1980)).

The finding that an LDT is a device is a sentinel determination enabling the Agency, at any time, to take enforcement action, to require registration, listing, compliance with quality systems, and premarket review and clearance or approval, at the Agency's discretion. Because this finding has significant economic effects on private interests, it raises the specter that the Agency, exercising discretion that is arguably not reviewable, could require laboratories to comply with any or all of these requisites that govern ordinary devices, the determination fits the profile of a legislative rule.[17] The Agency's determination that an LDT is a device "would be the basis for an enforcement action for violations of those obligations." *National Min. Ass'n, supra*. Consistent with that description, the Agency recently took action in the form of a Warning Letter against a laboratory based on its determination that an LDT is a device. *See* Warning Letter to Inova Genomics Laboratory (April 4, 2019). That Warning Letter is, to a reviewing court, convincing evidence that the decision to treat an LDT as a device was intended to have the force and effect of law and has been treated as such by the Agency.[18] Since the determination was issued without the benefit of notice and comment rulemaking, it is likely to be

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[17] The Agency's ever changing views of whether and when to exercise enforcement discretion could itself be viewed as a legislative rule. *See Am. Academy of Pediatrics v. F.D.A.*, 379 F.Supp.3d 461, 494 (D. Md. 2019), *affirmed on other grounds, sub nom. In re Cigar Association of America*, 2020 WL 2116554, at *3 (4th Cir. 2020).

[18] Whether a Warning Letter is an enforcement action or merely the first step in a compliance process is open to question in light of *Ipsen Biopharmaceuticals, Inc. v. Azar*, No. 18-5299 (D.C. Cir. Dec. 3, 2019). There are some who argue that FDA warning letters could be viewed as final agency action. Michelle Yeary, *Could FDA Warning Letters Be Final Agency Action*, DRUG & DEVICE LAW (Dec. 10, 2019), https://www.druganddevicelawblog.com/2019/12/could-fda-warning-letters-be-final-agency-action.html.

considered void if challenged.[19]

FDA has acknowledged that its issuances have the force and effect of law, even though its guidance documents trumpet the opposite in boilerplate. The Agency noted that it had exercised enforcement discretion with respect to LDTs, but that the 2014 draft guidances, when finalized, would have ended that. *See* Guidance Document at 6. Two years later, when abandoning the 2014 draft guidances, the Agency indicated its intent to continue extending enforcement discretion to LDTs, except in the event of a pandemic. See https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/information-laboratories-implementing-ivd-tests-under-eua (March 1, 2020) (last viewed June 15, 2020) ("FDA generally has not enforced premarket review and other legal requirements [with respect to LDTs]."). Obviously, an agency can only exercise enforcement discretion if it believes that it has the authority to enforce its determination, in this case that an LDT is a device.

C. FDA's Determination Is Inconsistent with Extant Departmental Regulations and Is Therefore Void Absent Notice and Comment Rulemaking

Third, if an agency adopts a position that is "inconsistent with an existing regulation, or effects 'a substantive change in the regulation,' notice and comment are required." *U.S. Telecom Ass'n v. F.C.C.*, 400 F.3d 29, 35 (D.C. Cir. 2005) (quoting *Shalala v. Guernsey Mem'l Hosp.*, 514 U.S. 87, 100 (1995)). Here, before FDA's initial determination in 1992 that LDTs are devices, the Secretary issued a comprehensive regulation implementing CLIA that expressly recognized three classes of laboratory tests—(i) those purchased by a laboratory that were FDA cleared or approved, (ii) those that are modifications of FDA cleared or approved tests, or (iii) "test system[s] not subject to FDA clearance or approval (including methods developed in-house [*i.e.*, LDTs] and standardized methods such as text book procedures . . .)." 42 C.F.R. § 493.1253(b) (2019) (adopted 68 Fed. Reg. 3640, 3707 (Jan. 24, 2003), previously codified at 42 C.F.R. 493.1213(b), 57 Fed. Reg. 7163 (Feb. 28, 1992)).[20] Those laboratories that use FDA cleared or approved tests are required to employ fewer quality controls than those laboratories that use modified tests or LDTs.

At bottom, the 1992 CLIA regulation recognizes LDTs as a separate class of tests not subject to FDA clearance or review, and by implication, FDA jurisdiction. That regulation is

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[19] Correspondingly, FDA has never performed a Regulatory Flexibility Act analysis, as would be required of significant substantive rules. FDA acknowledges that it did not perform any economic analyses of its guidances or of its determination that an LDT is a medical device. Dr. Shuren stated during the September 9, 2014, 21st Century Cures Act hearing that while the Agency had not conducted a formal economic impact analysis, and had no "hard numbers" of the cost to laboratories, the cost to laboratories should be manageable because laboratories should already have the clinical data in hand and the cost should primarily be sending in the data to FDA. 21st Century Cures hearing) (statement of Dr. Jeffrey Shuren, Director, CDRH, FDA); *see also id.* at 68.

[20] FDA's determination is also inconsistent with the Secretary's Medicare rules holding that a diagnostic laboratory test is a "service." *See, e.g.*, 42 C.F.R. § 410.32(d)(1). We understand that CMS has issued FAQs stating that LDTs are subject to FDA regulation. The FAQ is irrelevant as it is inconsistent with the plain language of CMS' 1992 and 2003 regulations, and potentially inconsistent with the Court's recent decision in *Azar v. Allina Health Services*, 139 S.Ct. 1804 (2019), requiring notice and comment rulemaking, rather than FAQs, with respect to any policy that may affect Medicare payment or eligibility to receive benefits or provide services or payment. *Allina* requires notice and comment rulemaking even in situations where the APA would not.

consistent with the legislative history underlying the 1988 amendments to the original Clinical Laboratory Improvement Act of 1967, which was limited to specimens traveling in interstate commerce. In supporting the 1988 amendments, Chairman Waxman noted the complete absence of federal regulation in certain instances: "many laboratories, particularly physicians' offices and smaller laboratories not accepting specimens in interstate commerce, are not subject to such Federal regulations."[21] FDA's determinations that LDTs are devices, none of which was published for notice and comment rulemaking, are inconsistent with this CLIA rule and the legislative history surrounding the 1988 amendments.

This inconsistency leads to one outcome for two alternative reasons. An interpretive rule or other policy issued without the benefit of notice and comment is *void ab initio* if it is inconsistent with an existing legislative rule. The legislative rule takes precedence over the interpretive one. *See F.C.C. v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) ("An agency may not, for example, depart from a prior policy *sub silentio* or simply disregard rules that are still on the books."); *Berkovitz v. United States*, 486 U.S. 531 (1988) (HHS is not free to ignore its own legislative rules); *Gunderson v. Hood*, 268 F.3d 1149, 1154 (9th Cir. 2001) (If a rule is inconsistent with or amends an existing legislative rule, then it cannot be interpretive."). Alternatively, the Agency determinations are void because they seek to modify or repeal an existing legislative rule which can only be accomplished through notice and comment rulemaking. *See Perez*, 575 U.S. at 105 ("APA rulemaking would still be required if [an agency] adopted a new position inconsistent with . . . existing regulations."); *Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Automobile Ins. Co.*, 463 U.S. 29 (1983).

Thus, even if none of the statutory impediments noted above existed, the Agency's determination that an LDT is a "device" would still falter for want of notice and comment rulemaking.

III. CLIA and Other Provisions in the PHS Act Can Provide Appropriate Safeguards

Regardless of the advice outlined above, we note, in light of concerns raised by some regarding dual regulation by FDA and CMS in this space, that the Secretary retains authority to ensure administrative efficiency by channeling regulation of LDTs through one agency and to determine which agency should exercise that authority. Policymakers may wish to consider whether CMS, which regulates through the Spending Clause and already regulates the actual use of tests in the laboratory, is better suited legally and logistically to regulate LDTs than is FDA, which is tethered by the Commerce Clause and by statutory commerce clause requirements.

One might take the position that Congress has addressed the federal regulation of laboratory testing in CLIA, and the Secretary has determined or can determine that CMS is the agency within HHS to regulate clinical laboratories. This is not to say that by enacting CLIA Congress expressed an intent that no further regulation was necessary. Rather, CLIA's comprehensive scheme arguably makes regulation by another HHS agency less essential. That is especially the case where the second agency's authority is relatively limited or vulnerable to legal challenge. In such situations, the other agency often provides technical assistance and that could be a model in this instance as well.

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[21] Clinical Laboratory Improvement Act, Hearing Before the Subcomm. on Health and the Environment, 100 Cong. 167, at 1 (1988). Representative Waxman's statement does not recognize any post-1976 role for FDA in the regulation of laboratories.

EXHIBIT G

AMERICAN CLINICAL LABORATORY ASSOCIATION

December 4, 2023

U.S. Food and Drug Administration
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: ACLA Comments on Proposed Rule, "Medical Devices; Laboratory Developed Tests" (Docket No. FDA-2023-N-2177)

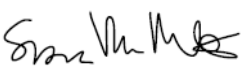
The American Clinical Laboratory Association (ACLA) submits the attached comments on FDA's Proposed Rule, "Medical Devices; Laboratory Developed Tests" (Docket No. FDA-2023-N-2177) ("Proposed Rule") which, if finalized, would subject laboratory developed tests (LDTs) to regulation as medical devices.

ACLA is the national trade association representing leading laboratories that deliver essential diagnostic health information to patients and providers by advocating for policies that expand access to the highest quality clinical laboratory services, improve patient outcomes, and advance the next generation of personalized care. ACLA member laboratories are at the forefront of developing tests to respond to emerging health issues, and they frequently innovate new areas of science. LDTs offered by ACLA members play an indispensable role in delivering healthcare to patients.

As detailed in the attached, ACLA has grave concerns with FDA's Proposed Rule, both as a matter of public policy and as a matter of law, and urges FDA to withdraw it. If implemented, the imposition of the ill-suited and rigid medical device authorities on LDTs would reduce patient access to widely used tests and dampen diagnostic innovations that improve and save lives. Over the past several years, ACLA worked collaboratively with FDA, Congress, and patient, provider, and diagnostic manufacturer stakeholders on legislation that could have established a role for FDA in an appropriate regulatory system for all diagnostics, complimentary to the already robust oversight of LDTs. ACLA's goal throughout that process was to develop a regulatory approach that would account for the unique attributes of laboratory diagnostics and which would strike the right balance between encouraging diagnostic innovation, maintaining access to important tests, and regulatory oversight. ACLA steadfastly maintains that legislation is the right – and only – approach for FDA to have a role in the regulation of LDTs. FDA's unilateral imposition of device law is misguided.

We would be pleased to further engage with FDA on any of the topics discussed in the attached comments.

Sincerely,



Susan Van Meter
President

COMMENTS OF THE
AMERICAN CLINICAL LABORATORY ASSOCIATION

Contents

EXECUTIVE SUMMARY

Laboratory developed tests (LDTs) are an indispensable pillar of our health care system, providing patients and physicians with diagnostic information to inform clinical care, power precision medicine, contribute to the discovery of novel therapeutics, and lead the fight against emerging pathogens. FDA's Proposed Rule — which would subject virtually all LDTs to medical device regulation – would significantly undermine the ongoing ability of laboratories to develop and offer innovative LDTs. If finalized, the rule would reduce patient access to LDTs, including those for which there are no FDA-cleared or -approved tests. It would also markedly diminish innovation in the next generation of diagnostics, including because device authorities are rigid and would not allow LDTs to keep pace with scientific advances. The Proposed Rule is also illegal: LDTs are not devices, and FDA lacks authority to regulate them as such. Accordingly, the Proposed Rule represents a regulatory overreach, and it should be withdrawn for multiple policy and legal reasons.

First, and most importantly, FDA's Proposed Rule would have significant adverse consequences for patients because it would undermine diagnostic and medical innovation and limit or eliminate access to critical tests. As described in Section I of these comments, the Proposed Rule would require laboratories to divert resources currently dedicated to research and development to focus on backward-looking activities in support of FDA approval for tests that have long been offered by laboratories and relied upon by physicians. Laboratories would be forced to examine test menus and make difficult decisions about which tests could support FDA submissions, likely resulting in the removal of low-volume tests, including for rare diseases, from test menus. That would also mean diverting resources away from the development of the next generation of diagnostics for cancer, infectious disease, cardiovascular disease, neurology, and numerous other diseases and conditions, including rare diseases and diagnostics for underserved communities, as well as diagnostics specifically developed for pediatric patients. The development of novel biopharmaceuticals would likewise slow. It would also mean reduced testing capacity, including for performance of IVDs, harming patient access to testing services, likely with disparate impacts for already underserved populations.

These added administrative burdens would be imposed at the very time when reimbursement for testing is being cut. While Congress recently enacted a one-year delay to Medicare payment cuts for clinical laboratory services, that is not a permanent solution. Year-over-year cuts are scheduled to be implemented starting January 1, 2025. At the same time, the costs of labor, equipment, and supplies are escalating, and a systemic workforce shortage for laboratory personnel persists.

The drain on innovation would be driven not just by the direct costs of FDA regulation (which would be significant), but also because the device framework is ill-suited and was never intended for LDTs. LDTs are services that rely on the expertise and judgment of trained medical and scientific professionals. Numerous aspects of device law — from the basic approval standards, to labeling and quality system requirements – do not fit LDTs. Moreover, the device regulatory system is rigid. The device premarket review system cannot account for the rapid evolution in diagnostic services occurring in oncology, neurology, infectious disease, and numerous other areas. Physicians and patients deserve testing services that incorporate the latest findings, including information reflected in clinical practice guidelines. Unlike FDA-regulated diagnostics, LDTs are able to accommodate the pace of change necessary to meet physician needs.

Consider oncology tests. In the oncology space, treating physicians rely on the professional services provided by laboratories because LDTs incorporate the latest scientific developments to inform the judgment of trained professionals, including diagnostic markers or combinations of

markers. Often these developments are reflected in the clinical literature or in well-accepted guidelines from professional organizations. In fact, several ACLA member laboratories that have obtained FDA approval for oncology tests have found that physicians turn to LDTs (sometimes offered by the same laboratories) because the FDA-approved versions might not include the latest advances in patient care. But device law would fundamentally change this paradigm by requiring lengthy premarket review for all or most such updates. Medical device authorities do not allow for the rapid innovation required to meet recognized scientific advancements and the standard of care. These barriers to innovation would add months or years to the development lifecycle for new LDTs – months and years that can make a life-or-death difference to a patient.

Innovation and access to testing services would also suffer because of the FDA-review bottleneck that device regulation would create, which would be orders of magnitude greater than what the Agency experienced during the COVID pandemic. FDA is not prepared – and would not be prepared – to regulate LDTs. Even using FDA's own estimates (which are based on assumptions and extrapolations, and are almost certainly low), the number of applications flooding into FDA would be staggering. FDA's estimates suggest that the initial number of premarket approval applications (PMAs) for LDTs would be greater than the cumulative number of original PMAs processed by FDA in the entire history – going back to 1976 – of medical device premarket review. Similarly, the annual number of PMA submissions would increase FDA's annual workload for diagnostics by over 500% (and that does not take into account other application types or other regulatory responsibilities). As we saw during the COVID pandemic, despite dedicated staff who strove to meet the challenge of a global pandemic, FDA lacks the resources to deal effectively with such surges in regulatory responsibilities. During the pandemic, resources had to be diverted from other parts of the Agency, and applications and interactions with FDA related to non-COVID diagnostics were placed on hold. FDA's promises that it can scale up resources ring hollow. Not only are FDA's resources limited, there simply are not enough trained scientists and regulatory professionals to go around, and FDA would be competing with laboratories that would also need to dramatically increase hiring of the same professionals (who are already in shortage) to deal with the new regulatory system. The impact of this rule, if finalized, would reverberate throughout the health care system, drawing away resources needed to advance medical product development.

Second, FDA's Proposed Rule paints a profoundly inaccurate picture of the essential testing services provided by laboratories. As explained in Sections II and III of these comments, FDA fails to consider the robust oversight that currently applies to laboratory testing services or the important public health contributions of LDTs. As explained in Section IV of these comments, FDA also uses unreliable and cherry-picked sources to mischaracterize laboratory testing services. In fact, laboratories and the LDTs they offer are subject to robust regulation under federal and state statutes, supplemented by rigorous accreditation standards and review by payers. Under that system, laboratories offering LDTs have delivered groundbreaking innovations that shifted the standard of care for diagnosis (and treatment) of important diseases; have been the first to respond to emerging public health threats; have played pivotal roles in the development of FDA-approved drugs, biologics, and other therapeutic products; and have offered critical tests for unmet needs in clinical care.

Rather than credit laboratories and their highly trained staff with these exceptional contributions to the public health, FDA's Proposed Rule paints a profoundly inaccurate picture. Even though FDA claims to be a data-driven agency, it did not systematically collect evidence to support the Proposed Rule. The "evidence" used to disparage LDTs is anecdotal and in many cases unverified, including selectively cherry-picked studies, unconfirmed allegations in lawsuits, complaints in the media and news stories, and claimed deficiencies in submissions. It is

disappointing that FDA took this approach, which it would never allow the regulated industry to use and which may undermine patient faith in laboratory testing.

Third, FDA's reliance on flawed data leads directly to the Agency's failure to appropriately assess the costs and benefits of the Proposed Rule, which is addressed in Section V of our comments. As FDA's Preliminary Regulatory Impact Analysis (RIA) acknowledges, FDA lacks data to properly consider the costs and benefits of the Proposed Rule. But it did not have to be this way: FDA has the regulatory tools to gather appropriate data to permit a more accurate assessment. FDA could have issued a Request for Information (RFI) to gather data on the number of laboratories that develop LDTs, the number of LDTs, the costs associated with research, development, and validation, as well as other categories of information. It also could have relied on the Centers for Medicare and Medicaid Services (CMS) to gather such data as CMS actively regulates clinical laboratories and LDTs. Instead of taking that approach, FDA assessed the costs and benefits of its proposed action using a series of unsupported assumptions and extrapolations.

To the extent that FDA has cited studies, those studies are flawed and/or misconstrued, leading FDA to underestimate the costs and overstate the claimed benefits of device regulation. As just one example, to estimate the claimed benefits of the proposed rule, FDA relies on a single study evaluating 19 oncology LDTs against FDA-approved companion diagnostics to broadly claim that 47% of all LDTs are "problematic." Then, FDA uses that 47% figure to extrapolate claimed benefits based on eliminating misdiagnoses from such problematic LDTs due to FDA regulation of all LDTs. There are many problems with this approach, not least of which is that the study FDA relies upon has been discredited. A recent and robust analysis of the same dataset demonstrates that the LDTs in the study performed as well as FDA-approved tests, undercutting FDA's argument that such tests are "problematic" and that FDA regulation would confer any benefits.

Likewise, FDA's cost estimates are significantly understated and do not take into account many of the most impactful costs associated with the rule. As discussed above, if finalized, the Proposed Rule would likely cause many important LDTs to be withdrawn – not because those testing services are "problematic," but because laboratories would lack the resources and time needed to develop and pursue FDA clearance or approval, and the very rigid and ill-suited nature of the medical device authorities would preclude many innovations from reaching patients. In fact, for the majority of LDTs, the burdens imposed by device regulation would significantly outweigh the value of FDA approval. Tests that serve small patient populations, such as for rare diseases, and those with modest reimbursement or revenue, may well be dropped from testing menus. Patients would suffer if these LDTs are no longer available. Failure to obtain a timely diagnosis would lead to increased morbidity and mortality, along with associated costs to our health care system and society more broadly. FDA's cost-benefit analysis fails to take these and other costs into account. An appropriate cost-benefit analysis, supported by accurate data, would demonstrate that the costs of imposing device law on LDTs would greatly exceed the benefits.

Furthermore, an assessment of FDA's RIA, drafted by Chris Carrigan, Global Economics Group, is attached as Exhibit 1 to these comments. As described in that analysis, the RIA fails to adhere to the standards in the Office of Management and Budget's (OMB) Circular A-4, which describes the standards for producing RIAs for rulemaking that would have a significant economic impact. This results in an economic assessment that fails on several dimensions. Among other problems, the RIA significantly understates costs by failing to quantify a key effect of the Proposed Rule and substantially inflates benefits by misusing benefit transfer methods. Furthermore, FDA fails to evaluate reasonable alternative regulatory approaches and offers minimal discussion of the distributional effects, including those on marginalized and underserved communities.

Ultimately, the record compiled by FDA does not support that LDTs are a significant public health problem to be fixed. Moreover, the proposed "solution" (device law) would cause numerous negative consequences for patients and our health care system. Unilateral imposition of device regulation on LDTs is the wrong solution in search of a problem.

Fourth, FDA's Proposed Rule is not just a bad public policy choice; it is illegal. As discussed in Section VI of these comments, FDA does not have legal authority to regulate LDTs as devices. The statutory authority to regulate devices delegated to FDA in the Food, Drug, and Cosmetic Act (FDCA), originally in 1938 and amended many times since, extends to physical products that are sold and distributed by manufacturers. But LDTs are services offered by trained laboratory professionals, not physical products. An LDT is a protocol or process by which a laboratory uses various tools – some of which are individually regulated as devices – to derive a test result for a patient. FDA's assertion that an LDT is a device is no less misguided than calling a surgery—performed by a physician using various tools (scalpels, sutures, etc.)—a device.

The development and performance of LDTs is regulated under a separate statutory and regulatory framework – the Clinical Laboratory Improvement Amendments of 1988 (CLIA) – and complementary state laws that interact with CLIA. The text of the FDCA, together with the legislative history and broader statutory framework of the FDCA and CLIA, make clear that LDTs are not devices and that Congress did not grant FDA authority to regulate LDTs. FDA's claim that it has authority over LDTs rests on an implausible assumption that an entire industry has been operating in violation of the FDCA for decades, and only now, after 85 years of device authority, has FDA decided to take action. FDA regulation of LDTs as devices would also raise significant concerns under the "major questions" doctrine and the First Amendment.

Finally, in Section VII of these comments, ACLA addresses the alternative approaches for which FDA solicited input, including (but not limited to) grandfathering, implementation timelines, recognizing existing programs such as that in New York State, and whether special treatment should be afforded to some test developers. While adopting some of these approaches could lessen the harm that would be created if the Proposed Rule were finalized, none would fix the fundamental legal and policy problems with imposing device law on testing services. The Proposed Rule would still exceed FDA's legal authority and would have significant negative consequences for the public health, as outlined in these comments. Furthermore, affording special treatment to only certain laboratories would raise additional legal concerns.

For all of these reasons, which are discussed in detail in the pages that follow, the Proposed Rule should be withdrawn. Rather than expending resources to finalize the Proposed Rule, if FDA seeks to establish additional oversight of LDTs, the Agency should engage with stakeholders, other HHS agencies, and Congress in a renewed effort to develop legislation that would establish appropriate regulatory authority for such additional oversight.

DISCUSSION[1]

I. Device Regulation is Wrong for LDTs and Would Undermine Innovation and Access to Diagnostic Testing.

In the Proposed Rule, FDA claims that it is "clarifying" that LDTs qualify as devices by adding ten words to the definition of an "*in vitro* diagnostic product" in 21 C.F.R. § 809.3 to state that such products "include[e] when the manufacturer of these products is a laboratory."[2] ACLA disagrees that the revised definition of "*in vitro* diagnostic product" in the Proposed Rule captures LDTs or that LDTs could qualify as devices.

Most fundamentally, the Proposed Rule reflects a misunderstanding of LDTs and the associated professional services provided by clinical laboratories. When understood that LDTs are services and not devices, it becomes abundantly clear that medical device regulation is the wrong fit for LDTs and applying such regulation would undermine diagnostic innovation and access to diagnostic testing for patients. Rather, LDTs have long been regulated under federal and state laws and subject to scrutiny by payers.

A. LDTs are professional services, not devices.

LDTs are unique assays designed, developed, and performed by clinical laboratories certified under CLIA to perform high-complexity testing (hereinafter "high-complexity laboratories") to yield important clinical information about a patient that can be used to inform or guide patient care. Laboratories that develop and perform LDTs are providing professional health care services; they are not acting as "manufacturers" and are not distributing devices. In short, LDTs are professional services; they are not devices.

As an example, consider the workflow associated with a mass spectrometry test offered by an ACLA member laboratory. After the test is ordered by a physician, a blood specimen is obtained by a phlebotomist and sent to the laboratory, and then laboratory staff complete the following tasks:

Pre-analytical steps

- Laboratory receives the blood sample and enters it into the laboratory information system (LIS)

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[1] All referenced material cited in these comments should be considered incorporated into ACLA's comments. ACLA would be pleased to provide copies of any cited references (subject to copyright or paywall limitations).

[2] Proposed Rule, *Medical Devices; Laboratory Developed Tests*, 88 Fed. Reg. 68006, 68031 (Oct. 3, 2023). In its preamble, FDA further alludes to its "traditional definition" of an LDT as a "test that is designed, manufactured, and used within a single laboratory that is certified under [CLIA] to perform high complexity testing" but states that "firms are offering IVDs as 'LDTs' even when they are not LDTs." 88 Fed. Reg. at 68009. ACLA does not agree with FDA's "traditional definition" of LDTs, which has never been stated in any statute, regulation or other document carrying the force of law. Today, LDTs are offered through a number of business models, including LDTs for which protocols are shared between laboratories under common ownership or LDTs that use third party service providers for certain analyses (e.g., bioinformatics). All of those models are consistent with CLIA and qualify as LDTs. FDA's Proposed Rule makes no attempt to distinguish among these models or provide a justification for regulating all such models in the same way.

- Laboratory staff completes pre-analytical steps per the relevant standard operating procedures (SOPs). This may include centrifuging the sample or aliquoting the sample into a separate tube for testing

Analytical steps

- Laboratory scientist prepares reagents, standards, quality control materials, and retrieves patient sample for testing
- Laboratory scientist performs daily maintenance on the instrument system to be used for sample preparation and testing
- Laboratory scientist pipettes applicable samples and reagents into 96-well plate
- Laboratory scientist performs extraction of the analyte(s) of interest using an automated liquid handling instrument
- Laboratory scientist builds the test run into the instrument software, such as specimen information, and loads samples onto testing system, which includes an automated sampler, liquid chromatography instrumentation, and high-resolution mass spectrometer
- When testing is complete, the laboratory scientist reviews the run qualitatively and quantitatively (e.g., chromatography and signal-to-noise ratios), including reviewing quality control to ensure results are within parameters for acceptable performance
- Laboratory scientist reviews patient results and utilizes software to determine concentration of the analyte(s) being measured and enters results into LIS

Post-analytical steps

- A second laboratory scientist or lead scientist reviews the results to confirm they were accurately interpreted, quantitated, and entered into the LIS
- The reviewing scientist approves results in the LIS, sending them electronically to the patient's electronic medical record
- The ordering clinician reviews the laboratory result produced by the test and uses it to inform clinician care decisions

This is an LDT: a series of tasks undertaken by trained laboratory professionals using instruments and other tools to derive information that may be useful to a treating physician. Under any reasonable interpretation, this is a service, not a device.

In contrast to LDTs, IVDs are manufactured products—instruments, reagents, materials, or any combination thereof—that are packaged, labeled and released by the manufacturer for use by a third party. IVDs are accompanied by instructions for use that inform the user how to use the device, and for IVD test kits, how to perform the test and what the results mean. They can be used by the persons identified in their label, whether that is the patient, a point-of-care provider, or a CLIA laboratory certified to perform the appropriate level of testing. Unlike LDTs, IVDs are products/articles that are commercially distributed to third parties. Because of this broad distribution, IVDs test kits present a greater potential for user error or other associated risks than LDTs. In contrast to IVDs, LDTs are developed specifically for use by the laboratory that created them, or laboratories under the same ownership/control, thereby promoting greater consistency in performance.

B. Applying device law would undermine innovation in diagnostics and access to critical testing services.

Imposing device law would limit the availability of breakthrough and high quality LDTs that advance patient care. As elaborated upon further below in these comments, LDTs drive medical innovation and advance patient care – they are often the best available testing option for patients and satisfy unmet needs in the absence of cleared and approved IVDs. However, as explained below, device regulation would harm patients by limiting diagnostic innovation, causing important tests to be removed from test menus, reducing access to testing services, and creating an untenable bottleneck at FDA that would prevent needed diagnostics from reaching patients.

1. Device regulation would slow innovation.

Device law would impose rigid requirements that are incompatible with LDTs and continued diagnostic innovation. Currently, laboratories can identify the need for a new clinical test, develop and validate that test, and introduce it within a matter of months. Then, because LDTs are services, trained laboratory professionals can fine tune and adjust the performance of LDTs to meet patient and physician needs. However, the rigid requirements of device law directly conflict with the flexibility under existing law that supports laboratories' ability to ensure that patients and providers receive the important diagnostic information they need. Several ACLA member laboratories that have obtained FDA approval for oncology tests have found that physicians prefer LDTs (sometimes offered by the same laboratories) because the FDA-approved versions might not include the latest advances in patient care. Medical device authorities do not allow for the rapid innovation required to meet recognized scientific advancements and the standard of care. The time to bring a new or modified test through FDA's clearance and approval process could delay patient access to otherwise validated tests by a matter of years. The end result is that patient care would lag behind scientific and medical advancements, which is not in the interest of public health.

a) Device regulation would divert limited laboratory resources.

As an initial matter, application of device regulation under the Proposed Rule would require laboratories to divert their already-limited resources away from research and development activities and toward FDA compliance activities, including re-validation of existing tests to support premarket submissions during the phaseout period. As discussed in detail further below, the cost of compliance with the Proposed Rule is significant – and significantly underestimated by FDA. During the phaseout period, laboratories would have to devote significant resources to developing and implementing policies and procedures to comply with Stages 1 through 3 of the phaseout policy and to the backward-looking exercise of re-validating existing tests and preparing premarket submissions. Even after the phaseout period, there are significant costs associated with ongoing compliance with device regulation. To satisfy these requirements, laboratory personnel and resources that are otherwise typically devoted to test development and innovation would be diverted to these FDA compliance activities. If existing resources are not diverted, then laboratories would need to hire additional personnel and purchase more resources.

Putting monetary cost aside, it is extremely unlikely that laboratories would be able to hire sufficient additional personnel. For the past several years, the laboratory industry has suffered from a devastating workforce shortage. At the April 2023 meeting of the Clinical Laboratory Improvement Advisory Committee (CLIAC), FDA acknowledged that laboratories desire tests with automation,

"especially high-throughput automation, because of workforce issues in your lab."[3] At the same meeting, a CLIAC member repeated that "workforce is the single most threat [*sic*] that we are experiencing right now in health care, not only with burnout, but with the pipeline is a key component to this."[4] And at the most recent CLIAC meeting in November 2023, the College of American Pathologists (CAP), an approved accreditation organization under CLIA, explained there are currently about 24,000 unfilled positions in laboratories across the country.[5] Staffing for existing needs has been a challenge for years, and increasing staffing requirements to satisfy FDA regulatory expectations is not likely to be feasible. The result is that laboratory innovation in diagnostics would grind to a halt during the phaseout period while resources are diverted to focus on device compliance activities and revalidation of existing tests.

b) Rigid and burdensome device requirements would slow diagnostic innovation.

Device law also would add rigid and burdensome validation and testing requirements that are not deemed necessary by existing regulatory frameworks, and this would lead to less innovation and slower development timelines, often without corresponding benefit to patients. Partly because the standard under device law is based on safety and effectiveness, which is not an appropriate standard for laboratory diagnostics,[6] and partly due to overly rigid approaches used by FDA, device law will add significant and unnecessary burdens to the development of new laboratory testing services using LDTs. Even assuming laboratories had the needed resources (which they do not, as explained above), and even assuming laboratories could shoulder the burdens of pursuing marketing submissions for all the new tests they develop (which they cannot, as explained further below), performing validation studies according to certain device special controls to support FDA clearance or approval can be prohibitively complex for LDTs. The end result is that important and innovative LDTs could not make their way through FDA's cumbersome device regulatory framework, and patients and providers would not receive important diagnostic information.

As an example of device special controls that are prohibitively complex for LDTs, consider genetic health screening tests. Genetic health screening tests require accuracy studies that include, *per variant and per sample-type*: 20 unique wild-type samples plus between 3 and 20 unique positive samples depending on whether the variant is heterozygous or homozygous, and its frequency in the population (as low as less than 0.1% to as high as greater than 2%).[7] While this might be manageable for a test for a single variant of a single gene using a single sample type, these requirements quickly become unmanageable for LDTs that analyze multiple genes representing tens of thousands of variants, and which accept multiple sample types. Moreover, these are the requirements for the accuracy study alone, and additional studies are still required for precision,

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[3] Clinical Lab'y Improvement Advisory Comm., *Meeting Transcript* 16 (Apr. 12-13, 2023, Atlanta, Georgia (Virtual)), https://www.cdc.gov/cliac/docs/april-2023/14-CLIAC_April-2023_Transcript.pdf.

[4] *Id.* at 122.

[5] Michael B. Datto MD PhD, CAP, Most common deficiencies – CAP Accreditation at 7 (Nov. 8-9, 2023), https://www.cdc.gov/cliac/docs/november-2023/10_CAP.pdf.

[6] In contrast, the New York State program (discussed below) uses a standard for diagnostics based on analytical and clinical validity. This was also the standard used in proposed legislation considered in recent years by Congress. ACLA believes that a standard focused on analytical and clinical validity would be a better fit for diagnostics than the device standard.

[7] 21 CFR § 866.5950.

determination of limit of detection, identification of interfering substances, and more. Simply locating the needed samples to perform these studies can be prohibitive, independent of the costs to perform the studies. Further, limiting FDA clearance to fewer variants is not an acceptable solution as this does not benefit the public health. For example, the first authorized cancer predisposition risk assessment system was cleared to identify only three variants on two BRCA genes.[8] However, a study comparing this test to an LDT found that the cleared test missed over 90% of BRCA mutations in persons who are not of Ashkenazi-Jewish descent and even 10% of BRCA mutations among persons who are.[9]

FDA often requires additional validation data that laboratories and other reviewing entities (*e.g.*, CLIA, CAP, New York State) have not determined to be necessary. For example, in the context of emergency use authorizations (EUAs) for MPOX diagnostics, a published report details how FDA's requests for additional validation studies or data did not meaningfully affect test performance and offered minimal benefits.[10] Laboratories have reported similar experiences with rigid FDA requirements in the context of COVID-19 EUAs. For example, one ACLA member recalled submitting stability data for the use of a particular swab in its EUA submission for a COVID-19 specimen collection kit for use with its laboratory test. Despite providing more stability data than the swab manufacturer ever provided to support clearance of the swab, FDA rejected the EUA request because the swab's stability data was not in the appropriate format. This rigid application of device standards slowed the availability of desperately needed testing.

FDA's approach to device regulation presents other serious barriers to innovation. To support companion diagnostic (CDx) approvals, FDA requires clinical concordance studies to other PMA-approved devices or clinical trials in partnership with drug companies. When a CDx has already been approved for a specific biomarker, there is no incentive for a drug company to conduct additional clinical trials to support diagnostic approvals. If the original CDx claim is held by a single-site LDT, there is no incentive for the laboratory with the approval to conduct clinical concordance studies with additional laboratories to support other diagnostic approvals. Broad regulation of LDTs is likely to put significant constraints on CDx availability, where doctors and patients would be forced to send samples to specific laboratories. A similar situation would occur for single-site LDTs that have 510(k) clearance. In many cases, validation studies would simply not be possible for additional laboratories who wish to offer tests that are substantially equivalent to a predicate LDT.

And even if validation studies were feasible, laboratories simply cannot afford to pursue marketing submissions for all LDTs. As explained further below in these comments, the costs of compliance with device regulation under the Proposed Rule would be significant, despite the fact that in many cases they would not improve the accuracy or reliability of LDTs. Additionally, because

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[8] *See* FDA, *Reclassification Order for DEN170046* (23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants)) (Jan. 17, 2019), https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170046.pdf.

[9] Neelam V. Desai et al., *Retrospective Cohort Study on the Limitations of Direct-to-Consumer Genetic Screening in Hereditary Breast and Ovarian Cancer,* 7 JCO PRECISION ONCOLOGY 1 (2023), https://ascopubs.org/doi/full/10.1200/PO.22.00695.

[10] JR Caldera et al., *FDA Trial Regulation of Laboratory Developed Tests (LDTs): An Academic Medical Center's Experience with Mpox In-House Testing*, 169 J. CLINICAL VIROLOGY 105611 (2023), https://www.sciencedirect.com/science/article/pii/S1386653223002342?via%3Dihub.

the device framework is rigid and defaults any "new" test to class 3—the highest risk classification—a greater number of LDTs would require PMA and De Novo submissions than have been estimated by FDA. A greater number also would require 510(k) submissions. The costs associated with these submissions also would be higher than FDA has estimated.

Given the high costs and challenges with adapting LDT services to comply with device regulation, laboratories may abandon efforts to develop novel tests if they cannot be demonstrated to be profitable. This is likely to have disparate impacts on vulnerable communities, including rare disease communities, that depend on the development and availability of LDTs. For example, genomic and other -omic technologies and applications as validated LDTs have been instrumental to identifying disease etiologies and encouraging research aimed at therapies. Such LDTs have led to the discovery of novel disease etiologies and improved diagnostic workups. Laboratories may not pursue such LDTs for clinical use, however, given the onerous validation requirements that would make offering such tests unprofitable. Instead, laboratories would have to prioritize pursuing development and marketing authorization for those tests and modifications that would be the most profitable and not necessarily those that would have the greatest clinical impact, particularly for small patient populations.

c) Device regulation would delay needed updates to cleared and approved tests.

Additionally, device regulation would limit laboratories' ability to offer modifications to cleared and approved tests, which are an important part of the clinical care services that laboratories offer to treating physicians. Currently, laboratories validate modifications to cleared/approved tests under CLIA and then make those modifications available to ordering providers. This has been important for adapting tests in unique circumstances, such as where a hospital laboratory may face practical challenges performing a test exactly according to its cleared/approved instructions for use, when there is a product or reagent shortage (or manufacturer recall) and different products or reagents must be validated for use, when the hospital needs to store specimens for longer periods prior to testing due to limited laboratory resources, or when the laboratory has upgraded to a higher throughput platform. Validating extended specimen stability specifications also has been critical for expanding access to tests for patients in underserved communities. It has also been of crucial importance to oncologists who expect to receive the most up-to-date information about genetic variants as relevant to treating cancer patients.

Most or all of these modifications would require, at minimum, a PMA supplement or new 510(k). In some cases, they may require entirely new PMAs or De Novo classification requests. This is supported by FDA's current guidance on 510(k) modifications. Under that guidance, a wide range of modifications to cleared tests would require new 510(k) notifications. FDA's guidance provides:

> Examples of changes in technology, engineering, or materials that likely alter the operating principle of the IVD and for which a new 510(k) is likely required include:
> - changes from radioimmunoassays ... to non-[radioimmunoassays];
> - changes in the antibody;
> - changes in detection reagents;
> - changes in critical reactions components; and
> - changes in conjugates.

> Examples of changes in technology, engineering, performance, or materials that might alter the operating principle of the IVD include:
> - changes from liquid to solid reagent;
> - changes in calibration materials and quality control materials;
> - changes in substrates;
> - changes in specimen type;
> - changes in specimen processing; and
> - changes in incubation times.[11]

The only modifications that the guidance identifies as not ordinarily affecting operating principles of the IVD are extremely limited, and include only:

> - changes to external packaging;
> - changes to use a new lot or batch for the same antibody or enzyme;
> - changes to a new vendor for the same reagent; and
> - changes in concentrations of packaged reagents provided the same diluted concentration was used in the assay.[12]

Clearly, FDA expects 510(k)s for any meaningful modification to a cleared or approved IVD, and the same would apply to modifications to cleared LDTs. Indeed, FDA has issued warning letters to IVD kit manufacturers who failed to submit 510(k)s for incremental improvements. For example, in November 2022, FDA issued a warning letter to an IVD manufacturer who made a reagent change to reduce interference in its assay to measure cardiac troponin I.[13] The standard for PMA supplements is even more stringent. A PMA supplement is required for any change that affects the safety or effectiveness of the device, including minor process changes that improve the performance of a test, or changes to a specimen tube in response to a supply chain shortage. Accordingly, modifications to approved LDTs would require frequent PMA supplements.

Predetermined change control plans (PCCPs) under new FDCA section 515C would not alleviate the need to submit 510(k)s and PMA supplements for modifications to cleared and approved IVDs. First, PCCPs only apply to changes that a manufacturer makes to its own device. It would not allow laboratories to adapt cleared/approved IVDs from other manufacturers to meet evolving clinical needs. Second, PCCPs only apply to those changes that the manufacturer can anticipate at the time of submission, and they do not afford a laboratory the ability to modify a cleared/approved test to meet evolving circumstances, such as product/reagent shortages or unique patient needs. Finally, PCCPs are a novel concept for FDA and industry, and it is unreasonable to expect laboratories not previously regulated by FDA to leverage tools that seasoned manufacturers are still grappling to

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[11] FDA, GUIDANCE FOR INDUSTRY & FDA STAFF, DECIDING WHEN TO SUBMIT A 510(K) FOR A CHANGE TO AN EXISTING DEVICE 39 (2017), https://www.fda.gov/media/99812/download.

[12] *Id.*

[13] FDA, *Warning Letter to Abbott Point of Care Canada Limited* (Nov. 8, 2022), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/abbott-point-care-canada-limited-640946-11082022.

understand. Ultimately, device regulation of LDTs would limit availability, slow innovation, and undermine incentives to improve existing tests.

d) Slowed innovation caused by applying device law would result in patient care lagging behind scientific and medical advances.

As demonstrated above, applying device law to LDTs would slow innovation. The detrimental impact to patients cannot be underestimated. This slowed innovation would cause patient care to lag behind established scientific and medical advances, many of which are recognized in clinical practice guidelines that represent the standard of care. Currently, high-complexity laboratories can validate methods under CLIA to measure biomarkers recommended under clinical practice guidelines or other peer-reviewed literature, and then report truthful and non-misleading information in test reports. In other words, laboratories can provide information that clinicians are requesting to inform patient care. However, device law limits the potential claims for a diagnostic intended to aid in therapy selection to those claims approved in drug labeling or a very limited subset of FDA-recognized sources, which will restrict laboratories from sharing this information until an FDA clearance or approval catches up with the recognized practice guideline or published literature. This would significantly slow innovation in the field of precision medicine, where the most up-to-date information on potential therapeutic options based on a patient's test results is often found in clinical practice guidelines.

Precision medicine in oncology would be hit particularly hard. Oncologists rely on LDTs to deliver diagnostic information consistent with emerging science, and new scientific discoveries are being made, and new clinical care guidelines are being published, faster than FDA can review and approve marketing submissions for diagnostics. For example, the National Comprehensive Cancer Network (NCCN) updates their guidelines on a continual basis, and is currently on its fifth version in 2023 for its guideline on non-small cell lung cancer.[14] By the time an oncology assay obtains approval or clearance, its clinical claims may not reflect the latest advances in patient care.

Moreover, as the sensitivity of instruments improves, and artificial intelligence/machine learning algorithms become more powerful, the pace of innovation in oncology is only expected to accelerate. Indeed, just last month (November 2023), a large diagnostic study of 43,524 individuals demonstrated that performing germline RNA sequencing (for which there are no approved or cleared IVDs) concurrently with DNA sequencing improves detection of novel variants and classification of existing variants.[15] And innovative LDTs are catching more high-risk genetic variants missed by cleared/approved tests.[16] Imposing device regulation on these assays would limit and slow patient and provider access to important diagnostic information based on the most current scientific

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[14] *See* NATIONAL COMPREHENSIVE CANCER NETWORK, NCCN GUIDELINES: NON-SMALL CELL LUNG CANCER, https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450 (current guideline "Version 5.2023").

[15] Carolyn Horton et al., *Diagnostic Outcomes of Concurrent DNA and RNA Sequencing in Individuals Undergoing Hereditary Cancer Testing*, JAMA ONCOLOGY e1 (2023), https://pubmed.ncbi.nlm.nih.gov/37924330/.

[16] *See, e.g.*, Susan Donaldson James, *At High Risk for Breast Cancer, Why This Woman Decided Against a Mastectomy*, TODAY (Oct. 11, 2016), https://www.today.com/health/breast-cancer-mutation-forces-women-make-hard-choices-t103717 (describing a woman whose BRCA mutation was identified by a test from a genetic testing company after an earlier test did not reveal the mutation).

evidence. That would be clearly at odds with the White House's Cancer Moonshot, a primary goal of which is to expand access to cancer screenings.[17] Time is of the essence to guide clinical care for oncology patients.

The bottom line is clear: applying ill-fitting device regulation to LDTs would slow diagnostic innovation to the detriment of patients.

2. *Medical device regulation would cause important tests to be removed from testing menus.*

Under device regulation, laboratories may not be able to continue offering important, currently available LDTs—not because such tests are not analytically or clinically valid, but because the device framework is overly rigid and the cost of compliance and premarket review could not be justified. As discussed above, device law imposes burdensome validation requirements that are not required under existing regulatory frameworks, and as explained further below in these comments, the costs of compliance with device regulation and pursuing premarket authorization is high – higher than FDA estimates. In some cases, laboratories may not be able to justify the cost of compliance and/or pursuit of marketing authorization for tests, and those tests would simply be removed from test menus and become unavailable to patients.

Most LDTs offered by laboratories do not generate significant revenues. Based on an informal survey of ACLA members, the majority of LDTs have annual revenues of less than $5 million. This is consistent with studies showing that while there are a significant number of LDTs that have been developed and are offered to patients, the rate at which LDTs are performed in the clinical setting is far lower than the rate at which approved and cleared IVDs are performed.[18] Accordingly, laboratories may not be able to financially justify pursuing marketing approval for all of the LDTs they have developed. Indeed, a substantial portion of LDTs bring in less revenue than the user fee submission cost alone for the test.

Tests that are able to generate only modest revenue, such as those for which there is a small patient population, are likely to be culled from test menus first. Many microbiology tests would be expected to fall into this category, as the combination of organisms and tests exponentially compounds what could reasonably be achieved in a marketing submission. These LDTs would be abandoned based on the high cost of pursuing premarket submissions and the minimal profit margin associated with such tests – not due to a lack of analytical or clinical validity. Many of the other tests that would be abandoned are rare disease tests and tests for pediatric populations.

Removing these tests from the market would have dire impacts for patients who rely on these LDTs. Absence of lower cost LDTs would limit access, thereby prolonging the diagnostic journey for many patients and depriving others of critical information that can guide efficient and effective care. The impact would be particularly pronounced for patients with rare diseases who rely on innovative LDTs where there is no cleared/approved alternative. A September 2023 study by EveryLife Foundation concluded that, on average, rare disease patients spend more than 6 years searching for

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[17] *The President and First Lady's Cancer Moonshot: Ending Cancer As We Know It*, THE WHITE HOUSE https://www.whitehouse.gov/cancermoonshot/ (last visited Nov. 7, 2023).

[18] *See* Jenna Rychert et al., *Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System*, 160 AM. J CLIN. PATHOL. 297 (2023), https://academic.oup.com/ajcp/article-abstract/160/3/297/7188944?redirectedFrom=fulltext.

a diagnosis, but an earlier diagnosis can avoid costs between $86,000 and $517,000 per patient cumulatively, in terms of medical costs and productivity loss in the pre-diagnosis years, during such period.[19] That earlier diagnosis is often available only with LDTs, but those LDTs may not be available under device regulation.[20]

In another study by Geno, et al., a hospital laboratory assessed the impact on its healthcare system when it was forced to discontinue its LDTs for immunosuppressant and definitive opioid testing (tests that are typically only available as LDTs) based on staffing constraints during the COVID-19 pandemic.[21] The study concluded that, although referral testing was available for some immunosuppressant testing, the extended turnaround times during the pandemic led to complications in the initial dosing of transplant patients. And discontinuing in-house opioid testing cost the health system over half a million dollars in the year since testing was discontinued.[22]

We note that FDA has acknowledged that application of device regulation under the Proposed Rule would result in some tests being removed from the market.[23] However, we think this is an unacceptable position for a public health agency. The public health is not protected by depriving patients of important tests. And indeed, FDA completely fails to consider the welfare costs to our healthcare system of having these tests become suddenly unavailable.

3. Device regulation would cause laboratory testing services, including for IVDs, to become more limited.

Diverting laboratory resources to compliance with medical device regulation under the Proposed Rule—both during the phaseout period and on and ongoing basis—also would harm patient access to diagnostic testing because fewer resources and personnel would be available to perform

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[19] EVERYLIFE FOUND. FOR RARE DISEASES, THE COST OF DELAYED DIAGNOSIS IN RARE DISEASE: A HEALTH ECONOMIC STUDY (2023), https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf.

[20] We disagree that such tests should be offered under the humanitarian device exemption (HDE) under FDCA section 520(m). First, the HDE for diagnostics is limited to tests where "not more than 8,000 patients per year would be subjected to diagnosis by the device in the United States." 21 CFR § 814.102(a)(5). Although a diagnostic may be intended to identify patients with a disease that affects no more than 8,000 patients, screening more than 8,000 patients would almost always be necessary. Indeed, even if a disease affects only 100 people in the United States, it may be necessary to test more than 8,000 patients per year to identify them. However, pursuing marketing approval for such a use would be cost prohibitive. Second, such exemption prohibits manufacturers from commercializing their assay except under narrow conditions. Developers innovating for patients with rare diseases should not be punished for their efforts.

[21] K. Aaron Geno & Mark A. Cervinski, *Impact of the Loss of Laboratory Developed Mass Spectrometry Testing at a Major Academic Medical Center*, 28 J. MASS SPECTROMETRY & ADVANCES IN THE CLINICAL LAB 63 (2023), https://doi.org/10.1016/j.jmsacl.2023.02.005.

[22] *Id.*

[23] 88 Fed. Reg. at 68,014 ("FDA also recognizes that some IVDs may need to come off the market, because … the laboratory chooses not to invest resources to meet those requirements."). It is wrong to suggest that laboratories would make this choice easily. Finalizing the Proposed Rule would force laboratories to make difficult choices about for which tests it can afford to pursue marketing authorization, and for which tests it cannot.

clinical testing services. As explained further above in these comments, there is a dire workforce shortage in the laboratory industry. In addition to diverting resources away from current innovation practices, resources would be diverted away from clinical testing services for patients, including clinical testing services for both LDTs and IVDs performed in that laboratory. Accordingly, patient access to clinical testing services—both for LDTs and cleared/approved IVDs—would suffer. Ongoing compliance costs would have a similar effect. Under FDA regulation, laboratories would be subject to dual inspections by FDA as well as CLIA/CAP/state regulators, further diluting existing resources.

Because laboratory resources are so limited, if/when laboratories identify tests that are worth the cost of pursuing FDA marketing authorization, they may be forced to divert resources typically used for clinical testing back toward research and development. Those personnel and facility spaces cannot be simultaneously used to perform tests for patients. For example, laboratories that modify existing test systems may need to dedicate instrumentation typically devoted to clinical testing to be used for clinical development. The laboratory may even have to cease testing using the cleared or approved version of the test while awaiting FDA review of its proposed modification.

Moreover, some laboratories may not be able to justify the cost of complying with the Proposed Rule and may close completely, depriving patients access to all testing that was offered by that facility. This is likely to have a disparate impact on already vulnerable and underserved communities whose access to testing services is already limited. It could also lead to consolidation in the testing market, reducing competition, driving prices upward, and making testing services less accessible to patients.

Finally, we must stress that laboratories are already stretched exceedingly thin in terms of resources, including personnel. As discussed earlier, there is an ongoing shortage of laboratory professionals available to support testing services and development of new assays. Moreover, laboratories are facing significant cuts to payment for their services under the Protecting Access to Medicare Act (PAMA) of 2014.[24] All of these factors, together with application of ill-fitting device regulation to LDTs, converge to threaten the continued existence of many laboratories, which is not in the interest of public health, particularly when, as FDA noted in the Proposed Rule, 70% of medical decisions are based on laboratory test results. FDA failed to consider these costs to our healthcare system.

4. *FDA is not prepared to regulate LDTs as devices, which would cause innovation to slow across the industry.*

Under the Proposed Rule, FDA anticipates receiving all PMAs 3.5 years after the phaseout period is finalized, and all De Novo classification requests and 510(k)s 4 years after the phaseout period is finalized. These initial premarket submissions, as well as ongoing submissions expected on an ongoing basis thereafter would slow patient access to innovative tests as FDA deals with an overwhelming increase in workload, leading to extended review times and fewer FDA resources to engage with applicants and developers. Moreover, FDA is likely to face the same or similar staffing challenges as both the Agency and laboratories compete for limited specialized talent amidst an

[24] While Congress recently enacted a one-year delay to Medicare payment cuts for clinical laboratory services, that is not a permanent solution. Year-over-year cuts are scheduled to be implemented starting January 1, 2025.

existing workforce shortage. And FDA is likely to continue struggling, even after the initial bolus of regulatory submissions.

a) FDA is not prepared for the avalanche of submissions it would receive for existing tests, and this would slow innovation across the industry.

First, at years 3.5 and 4 of the phaseout period, premarket submissions would flood into the Agency, and FDA reviewers would be overwhelmed with reviewing these submissions. Even if FDA's low estimates were correct, it would receive 4,210 PMAs, product development protocols (PDPs), and Panel-Track PMA Supplements (collectively "PMA Submissions"), 4,020 De Novos, and 32,160 510(k) submissions all at once at years 3.5 and 4 of the phaseout period. This is an overwhelming amount of work for the Agency. In its entire history since the enactment of the Medical Device Amendments of 1976 (48 years), FDA has only approved 302 original PMAs and Panel-Track PMA Supplements for IVDs, 135 De Novos for IVDs, and 30,178 510(k)s for IVDs.[25]

The RIA itself acknowledges that FDA typically processes on average in a given year: 73 PMA Submissions; 66 De Novo requests; and 3,877 510(k)s. Based on FDA's own estimates, however, it would experience an increase in submissions of more than 5,000 percent for PMA Submissions, more than 6,000 percent for De Novos, and more than 800 percent for 510(k)s during stages 4 and 5 of the phaseout period. FDA would be expected to review *all* of these premarket submissions—plus IVD kit submissions that are expected to continue to be submitted. Moreover, FDA would be expected to conduct preapproval inspections for all class III LDTs requiring PMAs. Regardless of what is negotiated in the next Medical Device User Fee Amendments (MDUFA) cycle, this would be a herculean amount of work for FDA – work that FDA is unlikely to be able to find the resources to complete.

With regard to resources, FDA would need to begin hiring reviewers to support these applications far in advance of when user fees would be paid. Accordingly, FDA cannot brush off the increase in workload by pointing to the next MDUFA cycle and asserting that costs would be borne by the industry. Taxpayer funds would be necessary to support FDA's activities, and the Agency has failed to provide an assessment of the costs it would impose on the country. And even if FDA had the funds to hire new reviewers, we expect that FDA would struggle to hire additional reviewers for the same reasons that laboratories would struggle to hire additional laboratory professionals.

We also disagree that FDA's 510(k) Third Party Review Program would significantly alleviate this burden. Such program does not extend to PMAs and De Novos, and as explained earlier, most novel LDTs would require authorization through one of these pathways. Furthermore, there are currently only seven approved third party review organizations, and four of those organizations (i.e., more than half) review fewer than 40 of the hundreds of types of IVDs that may be cleared under a

[25] These numbers are gathered from FDA's PMA, De Novo and 510(k) databases and downloadable files. The PMA database search included all approvals for original PMAs and Panel-Track PMA Supplements for IVDs (approvals for PDPs are not publicly available). The De Novo database search included all De Novo classifications within the panels for Immunology, Microbiology, Clinical Chemistry, Pathology, Toxicology, Hematology, and Molecular Genetics, and accordingly, may even be an overestimate. The 510(k) database search required download of available 510(k) files, sorted to include 510(k) clearances for advisory committee categories of Immunology, Microbiology, Clinical Chemistry, Pathology, Toxicology, Hematology, and Molecular Genetics, and accordingly may even be an over estimate. These searches were conducted on November 10, 2023.

510(k).[26] Finally, such program has long been criticized by industry because the high rate of re-review by FDA means that utilization of such program can actually extend premarket review time.[27] Accordingly, applicants are unlikely to rely on such program for clearance of LDTs.

Any traditional IVD premarket submission submitted around or after years 3.5 and 4 of the phaseout period would necessarily be caught in FDA's guaranteed backlog. This means IVD manufacturers would also struggle to roll out new tests, slowing patient access to these tests, as well. This happened during COVID, when FDA was completely overwhelmed with EUA submissions from laboratories and FDA could not manage its regular IVD workload. During that time, FDA stopped reviewing all IVD presubmissions that were not related to COVID-19, a companion diagnostic, a breakthrough designation request, or otherwise had a significant public health impact.[28] Non-COVID-19 IVD files also experienced significant delays in initiation of review.[29]

Furthermore, even before premarket submissions are required for LDTs at years 3.5 and 4 of the phaseout period, FDA would be flooded with presubmission requests from laboratories seeking guidance on risk classification and how to pursue marketing authorization for their tests. Compliance with FDA regulation is new for most laboratories, and laboratories would have numerous questions about the classification of potential tests (e.g., is a PMA or a De Novo more appropriate?) as well as the validation studies needed to support ultimate marketing authorization. Such presubmission requests, for which FDA does not receive revenue from a user fee, would be submitted before the next MDUFA cycle, meaning FDA would have to address such requests with its existing, limited resources. Diverting those FDA resources to LDT presubmissions would also negatively affect IVD manufacturers, as FDA would likely miss MDUFA goal dates for review of IVD presubmissions *and* premarket submissions during the phaseout period. This means a slower pace for bringing innovative tests to patients, regardless of whether those tests were developed by laboratories or commercial manufacturers.

This flood of presubmissions cannot be addressed through guidance documents, either. The Proposed Rule states that FDA intends to release additional guidance documents during the transition period, but in order for laboratories to benefit from such guidance documents when performing re-validation of tests, the guidance documents would need to be released almost immediately after publication of the final rule. Furthermore, even if such guidance documents were timely released, it is unreasonable to expect that such guidances would address every question from laboratories. Instead, FDA would be flooded with presubmission requests from affected laboratories upon release of the final rule, further depleting laboratory and FDA resources.

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[26] Current List of FDA-Recognized 510(k) Third Party Review Organizations. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/accredit.cfm (last visited Nov. 30, 2023).

[27] *See, e.g.*, Brian J. Miller et al., *The 510(k) Third Party Review Program: Promise and Potential*, 47 J. MED. SYSTEMS 93 **(**2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10465388/ ("Utilization declined form a peak of 9.3% in 2008 to 2.4%, a decline due to a multitude of factors," including FDA re-reviews).

[28] FDA, *A Year Into the Pandemic: How the FDA's Center for Devices and Radiological Health is Prioritizing its Workload and Looking Ahead* (Apr. 15, 2021), https://www.fda.gov/news-events/fda-voices/year-pandemic-how-fdas-center-devices-and-radiological-health-prioritizing-its-workload-and-looking.

[29] *Id.*

b) FDA is not prepared for the increase in workload for new and modified tests, and this would slow innovation across the industry.

Second, even after the initial flood of applications and the phaseout period is complete, FDA would continue to be vastly overwhelmed by marketing submissions for new LDTs and modifications to cleared and approved tests. The RIA estimates that each year, FDA would receive 407 PMA Submissions, 389 De Novo requests, and 3,110 510(k) submissions. But, as explained later these comments, this is a significant underestimate.

Even if FDA's low estimates were correct, however, FDA would be overwhelmed by this increase in submissions. As noted earlier, FDA typically processes on average in a given year: 73 PMA Submissions; 66 De Novo requests; and 3,877 510(k)s. Based on FDA's own estimates, however, it would experience an annual increase in submissions of more than 500 percent for PMA Submissions, more than 500 percent for De Novos, and more than 80 percent for 510(k)s. This significant increase in workload is unlikely to be met with an increase in personnel, particularly in light of the laboratory professional workforce shortage. For the reasons stated above, we continue to disagree that the 510(k) Third Party Review program would significantly alleviate this burden.

Traditional IVD premarket submissions also would be caught in FDA's guaranteed backlog, which would also slow the ability of IVD manufacturers to roll out new tests, slowing patient access to these tests, as well. And as explained earlier, FDA's workload would be further compounded by presubmission requests as laboratories unfamiliar with device regulation learn to navigate the device framework, and this increase in workload is unlikely to be alleviated through the release of guidance documents.

For all of these reasons, device regulation would undermine diagnostic innovation and patient access to critical tests. Applying device regulation to LDTs is the wrong approach.

II. LDTs Are Subject to Robust Regulation and Review.

FDA issued its Proposed Rule amidst the backdrop of its long history of not regulating LDTs and taking inconsistent positions on LDTs. In contrast, Congress and states have implemented a clear system for regulating laboratories and LDTs for decades that promotes their accuracy and value. The Proposed Rule mentions but does not fully describe the oversight that has long been applicable to laboratories and LDTs via CLIA, state laws, and scrutiny by public and private payers. FDA has failed to provide a reasoned basis for such regulation being insufficient or an inadequate framework to address any concerns.

Below we first describe FDA's vacillating position on LDTs and then describe the robust oversight that currently exists for laboratory testing services.

A. FDA's history of inconsistent positions on LDTs.

FDA has had authority under the FDCA to regulate medical devices since 1938, and in the Medical Device Amendments of 1976 (MDA) Congress significantly expanded those authorities. But in neither of those statutes, nor in any subsequent amendment to the FDCA, did Congress assign the regulation of LDTs to FDA, nor has Congress appropriated the funding or provided for user fees that could support such an expansion of FDA's authority. Instead, Congress enacted a wholly different framework to regulate laboratory services, including the development of LDTs. Congress enacted the Clinical Laboratory Improvement Act of 1967, assigning the role of regulating laboratory services to (what is now called) the Centers for Medicare and Medicaid Services (CMS). Confirming that

understanding, Congress again addressed laboratory testing by strengthening CMS's role through enactment of the Clinical Laboratory Improvement Amendments of 1988. Indeed, CLIA '88 was enacted by Congress specifically to strengthen the oversight of LDTs. But nowhere in the legislative history of CLIA '67 or CLIA '88 did Congress suggest that FDA had any regulatory role over LDTs as devices. In fact, FDA was never even considered.[30]

FDA did not even claim the authority to regulate LDTs until nearly 60 years after the enactment of the FDCA and 20 years after the MDA. In a 1992 draft Compliance Policy Guide (CPG), FDA alluded to "laboratories … manufacturing [LDTs] … and utilizing these unapproved products for diagnostic purposes." FDA never finalized that CPG. Four years later, in a regulatory preamble to a proposed rule that would regulate not LDTs, but analyte specific reagents (ASRs – which are components used in diagnostic tests), FDA mentioned that it had not "actively regulated" LDTs and might do so in the future.[31] But in the preamble to the Final Rule regarding ASRs, FDA explained that LDTs "contributed to enhanced standards of medical care in many circumstances and … significant regulatory changes in this area could have negative effects on the public health," and FDA imposed no meaningful regulatory requirements on LDTs.[32]

Since that time, FDA has claimed at various points that it has authority to regulate LDTs as devices, but it has never actually exercised that claimed authority in a comprehensive manner. In 2006 and 2007, FDA proposed to regulate a subset of LDTs that use software by issuing two different draft guidance documents.[33] That effort was abandoned. FDA then claimed authority over narrow categories of tests and some laboratories have acquiesced to FDA's claimed authority.[34] The last time FDA proposed to comprehensively regulate LDTs, via draft guidance documents in 2014, the Agency never followed through, and the draft guidance documents were never finalized. In recent years, even the position within HHS has vacillated regarding FDA's authority to regulate LDTs as devices. Just three years ago, an HHS legal memorandum was made public in which the General Counsel of HHS acknowledged significant limitations on FDA's ability to regulate LDTs.[35]

Confirming that FDA currently lacks authority over LDTs, Congress has long considered whether to grant FDA new authority to regulate LDTs under a non-device framework. The most recent effort was Congress's consideration of the Verifying Accurate Leading-edge IVCT

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[30] The legislative history of the FDCA and CLIA are further addressed in Section VI.A.2 of these comments.

[31] Proposed Rule, *Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents*,61 Fed. Reg. 10484, 10484 (Mar. 14, 1996).

[32] Final Rule, *Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents*, 62 FR 62243, 62249 (Nov. 21, 1997).

[33] FDA, DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, AND FDA STAFF: *IN VITRO* DIAGNOSTIC MULTIVARIATE INDEX ASSAYS (2007), https://www.fda.gov/media/71492/download; FDA, DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, AND FDA STAFF: *IN VITRO* DIAGNOSTIC MULTIVARIATE INDEX ASSAYS (2006), https://www.govinfo.gov/content/pkg/FR-2006-09-07/pdf/06-7499.pdf.

[34] These categories include companion diagnostics, direct-to-consumer tests offered without a prescription, tests offered during a public health emergency, and certain pharmacogenomic tests.

[35] *See* Robert Charrow, HHS General Counsel, Federal Authority to Regulate Laboratory Developed Tests (June 22, 2020) ("Charrow Memorandum"), https://www.politico.com/f/?id=00000174-e9b2-d951-a77f-f9fe04fa0000.

Development (VALID) Act, which was debated as part of the Consolidated Appropriations Act of 2023, and re-introduced as recently as March of this year. The VALID Act would have established a new product category under FDA's jurisdiction—*in vitro* clinical tests (IVCTs)—that would have included both IVDs and LDTs. If LDTs were devices, this legislation would be unnecessary. Congress's serious consideration of this legislation in 2022 confirms that Congress never provided FDA authority to regulate LDTs as devices.

Notwithstanding this history, FDA is once again asserting that Congress granted it regulatory authority over LDTs using its device authorities. However, as explained further below, this is wrong (Congress granted FDA no such authority), and as explained above it is an ill-advised policy position that stands to harm patient health (device law would undermine innovation and patient access to important LDTs).

B. CLIA applies to all clinical laboratories and LDTs.

CLIA establishes a framework for the regulation of laboratories and laboratory testing services—including LDTs. CLIA requires that all LDTs are developed and performed only in laboratories certified to perform high-complexity testing and under the direct control and supervision of highly trained clinical laboratory professionals.

1. Under CLIA, laboratories rely on the expertise of highly trained professionals.

Under CLIA, high-complexity laboratories that develop and perform LDTs are overseen by a laboratory director, the majority of whom are licensed physicians in the state, and the rest of whom hold an earned doctoral degree in chemical, physical, biological or clinical laboratory science and a certification by an HHS-approved board.[36] Moreover, CLIA requires that a laboratory may also require support from: (1) a technical supervisor, who has additional training or experience in high-complexity testing within the particular specialty or subspecialty of testing performed by the laboratory;[37] and (2) a clinical consultant qualified to consult with and render opinions to the laboratory's clients concerning the diagnosis, treatment and management of patient care.[38] The clinical consultant must either meet qualifications equivalent to a laboratory director, or otherwise be a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine licensed to practice in the state.[39] And all high-complexity testing personnel must either (a) be a licensed physician,

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[36] *See* 42 CFR § 493.1443. The HHS-approved boards include the American Board of Bioanalysis (ABB); ABB public health microbiology certification; American Board of Clinical Chemistry (ABCC); American Board of Forensic Toxicology (ABFT); American Board of Medical Genetics and Genomics (ABMGG); American Board of Medical Laboratory Immunology (ABMLI); American Board of Medical Microbiology (ABMM); American College of Histocompatibility and Immunogenetics (ACHI); National Registry of Certified Chemists (NRCC); and Diplomate in Medical Laboratory Immunology (DMLI). HHS, *GUIDANCE: CERTIFICATION BOARDS FOR LABORATORY DIRECTORS OF HIGH COMPLEXITY TESTING* (2020), https://www.hhs.gov/guidance/document/certification-boards-laboratory-directors-high-complexity-testing#:~:text=The%20qualification%20for%20a%20laboratory%20director%20of%20high,be%20certified%20by%20a%20board%20approved%20by%20HHS.

[37] 42 CFR § 493.1449.

[38] *Id.* § 493.1455.

[39] *Id.*

(b) have earned a doctoral, master's or bachelor's degree in a chemical, physical, biological or clinical laboratory science, or medical technology, or (c) have earned an associate degree in laboratory science or medical laboratory technology, or equivalent education and training.[40] Accordingly, laboratory developed testing services are performed only by highly skilled and trained laboratory professionals.

The responsibilities of the laboratory director and clinical consultant underscore the value of the services provided by clinical laboratories. In addition to overseeing the operation and administration of the laboratory, the laboratory director is responsible for ensuring that selected test methodologies "have the capability of providing the quality of results required for patient care," "reports of test results include pertinent information required for interpretation," and "consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific conditions."[41] The clinical consultant is expressly responsible for "provid[ing] consultation regarding the appropriateness of the testing ordered and interpretation of test results."[42]

These activities of the laboratory director, clinical consultants, and other professionals employed by laboratories, such as accredited genetic counselors, all may fall within the practice of medicine, and are recognized under state laws as such.[43] These activities are core to the professional services provided by laboratories that enable ordering providers to provide the highest quality clinical care for their patients.

2. CLIA imposes strict quality requirements and proficiency standards.

Additionally, development and performance of LDTs are subject to strict quality controls under CLIA. When an LDT is developed, high-complexity laboratories must "before reporting patient results, establish for each test system the performance specifications for the following performance characteristics, as applicable: (i) Accuracy. (ii) Precision. (iii) Analytical sensitivity. (iv) Analytical specificity to include interfering substances. (v) Reportable range of test results for the test system. (vi) Reference intervals (normal values). (vii) Any other performance characteristic required for test performance."[44] Indeed, these requirements apply specifically when a laboratory modifies an FDA-cleared or -approved test or develops "a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book

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[40] *Id.* § 493.1487.

[41] *Id.* § 493.1445(e)(3)(i), (e)(8) - (e)(9).

[42] 42 CFR § 493.1457.

[43] *See, e.g.*, Utah Code Ann. §§ 58-67-102(19)(a) ("Practice of medicine" means "(i) to diagnose ... by any means or instrumentality") & 58-67-102(12)(a) ("Diagnose" means "to examine in any manner another person, parts of a person's body, substances, fluids, or materials excreted, taken, or removed form a person's body, or produced by a person's body, to determine the source, nature, kind, or extent of a disease or other physical or mental condition").

[44] 42 CFR § 493.1253(b)(2) (requirement to establish performance specifications for a modified FDA-cleared or approved test system or "a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures)").

procedures)."[45] Then, like all other non-waived tests performed in the high-complexity laboratory, the LDT remains subject to the laboratory's extensive quality system that requires, among other things, establishment and performance of calibration and control procedures, maintenance and function checks for equipment, instruments, and test systems, and on-going quality monitoring.[46]

CLIA further requires that laboratories enroll and participate in approved proficiency testing programs, which serve as external quality control programs for laboratories.[47] Proficiency testing requires that the laboratory test blinded samples according to their typical laboratory procedures and report the results back to the approved proficiency testing program for evaluation. The laboratory successfully participates in proficiency testing if it obtains the testing scores outlined in CLIA regulations, and fails if it does not obtain such scores.[48] Importantly, the laboratory must participate in proficiency testing "for each specialty, subspecialty, and analyte or test in which the laboratory is certified under CLIA."[49] If the laboratory fails to successfully participate in proficiency testing, then CMS may impose sanctions, including suspension, limitation, or revocation of the CLIA certificate.[50] If a test offered by the laboratory is not included in an approved proficiency testing program, as may happen with a novel LDT, then the laboratory must verify the accuracy of such test at least twice annually.[51] Studies have found that LDTs developed under the CLIA framework can perform as well or better than FDA-cleared or approved test kits.[52]

3. CLIA is supplemented by rigorous accreditation standards.

CLIA sets a minimum standard applied to clinical laboratories, but many laboratories are subject to more stringent requirements imposed by their accrediting organization. Under CLIA, laboratories can receive certification for high-complexity testing via either a certificate of compliance based on compliance with the CLIA regulations as written, or via a certificate of accreditation based on compliance with the requirements of a CMS-approved accreditation organization.[53] To be

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[45] *Id.*

[46] *Id.* §§ 493.1200 - 493.1299.

[47] 42 CFR §§ 493.801 - 493.807.

[48] *See id.* §§ 493.821 - 483.865.

[49] *Id.* § 493.801(a).

[50] *Id.* §§ 493.803(b), 493.1806.

[51] *Id.* §§ 493.801(a)(2)(ii), 493.1236(c)(1).

[52] *See, e.g.*, Gilad Vainer et al., *Equivalence of Laboratory-Developed Test and PD-L1 IHC 22C3 pharmDx Across All Combined Positive Score Indications*, 18 PLoS ONE 1 (2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10237432/; Annette S. Kim et al., *Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing*, 4 JAMA ONCOLOGY 838 (2018), https://jamanetwork.com/journals/jamaoncology/fullarticle/2665746; Joel T. Moncur et al., *Performance Comparison of Different Analytic Methods in Proficiency Testing for Mutations in the BRAF, EGFR, and KRAS Genes: A Study of the College of American Pathologists Molecular Oncology Committee*, 143 ARCHIVES PATHOLOGY & LAB'Y MED. 1203 (2019), https://meridian.allenpress.com/aplm/article/143/10/1203/420696/Performance-Comparison-of-Different-Analytic.

[53] *See* 42 U.S.C. § 263a(d).

approved, however, the accreditation organizations must apply standards "equal to or more stringent than the standards" under CLIA.[54] And indeed, accreditation organization standards generally are more stringent than the standards under CLIA. For example, the College of American Pathologists (CAP) is more prescriptive regarding methods for establishing performance specifications for LDTs,[55] and specialty CAP checklists often have additional, specific requirements for analytical validation of tests within a specialty.[56] CAP specifically requires that laboratories clinically validate all LDTs using either (i) a clinical validation study, generally consisting of at least 20 samples or (ii) peer-reviewed literature.[57] The specialty CAP checklist for molecular pathology specifically states that "[i]t is essential that the laboratory director or designee use professional judgment in evaluating the results of [clinical validation] studies and in monitoring the state-of-the-art worldwide as it applies to newly discovered gene targets and potential new tests, especially those of a predictive or incompletely penetrant nature."[58]

C. State laws impose additional requirements on laboratory testing services.

Clinical laboratories are subject to additional requirements under state laws. For example, Florida imposes additional licensing requirements for laboratory personnel operating in the state.[59] Moreover, some states like California, Maryland, New York, Pennsylvania, and Rhode Island impose additional licensing and permitting requirements for *any* laboratory that offers testing on specimens from those states.[60] These requirements extend beyond the laboratories within those states to laboratories across the country if that laboratory offers tests to the state's residents.

New York's clinical laboratory law warrants special attention. Any laboratory testing specimens from New York patients, whether located in New York or not, must obtain approval of

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[54] *Id.* § 263a(e)(2)(A).

[55] COLL. AM. PATHOLOGISTS, CAP LABORATORY ACCREDITATION PROGRAM ALL COMMON CHECKLIST COM.406350 (Validation of Test Performance Specifications – Modified FDA-cleared/approved tests and LDTs) (2023).

[56] *See, e.g.*, COLL. AM. PATHOLOGISTS, CAP LABORATORY ACCREDITATION PROGRAM CHEMISTRY AND TOXICOLOGY CHECKLIST CHM.13750 (Cut-Off Values for Qualitative Tests) (2023),; COLL. AM. PATHOLOGISTS, CAP LABORATORY ACCREDITATION PROGRAM MOLECULAR PATHOLOGY CHECKLIST MOL.31015 (Validation Studies – Specimen Types) (2023).

[57] COLL. AM. PATHOLOGISTS, *supra* note 55, at COM.40625 (Clinical Claims Validation – FDA-cleared/approved Tests) and COM.40640 (Clinical Performance Characteristics Validation – Laboratory-developed Tests).

[58] COLL. AM. PATHOLOGISTS, CAP LABORATORY ACCREDITATION PROGRAM MOLECULAR PATHOLOGY CHECKLIST, *supra* note 56, at MOL.31590 (Clinical Performance Characteristics).

[59] Fl. Stat. § 483.813 ("A person may not conduct a clinical laboratory examination or report the results of such examination unless such person is licensed under this part to perform such procedures.").

[60] Cal. Bus. & Prof. Code § 1241(a); Md. Code Health § 17-215(a); NY Pub. Health Law § 574; 35 Penn. Stat. § 2163.1(a); RI Stat. § 23-16.2-4(a).

individual LDTs, consistent with its risk classification, from state authorities.[61] To obtain New York approval to perform an LDT, the laboratory must satisfy the applicable general standards and specialty standards for a test,[62] and submit a full method validation, including information specified in a general or specialty-specific checklist, and a risk attestation form.[63]

The method validation requires submission of detailed information for the state's review. For example, for molecular genetic testing, laboratories are required to include a description of the test, information regarding specimen and requisition requirements, information about materials and methods (including reagent recipes, a step-by-step protocol, assay controls, and more), validation data, and information about results and interpretation.[64] The risk attestation requires submission of additional information including: for clinical claims or direct references to recognized diseases/conditions, full citations to references or supporting clinical or laboratory data and/or publications if clinical trials/studies were performed; an explanation of which critical and/or essential information (if any) is generated to inform or influence treatment of a patient; and a description of the potential impact of an inaccurate result.[65] These requirements are robust, but they are efficient – the amount of data required by New York is less than would be required by FDA under device law, yet it is sufficient to evaluate the analytical and clinical validity of the tests.

D. Payers scrutinize LDTs for coverage decisions.

The clinical validity of tests is also closely scrutinized by both public and private payers. For example, the Molecular Diagnostic Program (MolDX) provides Medicare coverage for molecular diagnostic tests, including LDTs, only once those tests have demonstrated analytical validity, clinical validity and clinical utility.[66] To obtain coverage, laboratories must submit dossiers with scientific

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[61] NYCRR § 58-1.1(a)(1)(iv) (requiring that "all tests performed in New York State or on specimens from New York State are either: (a) classified as approved, cleared, or exempt by the United States Food and Drug Administration (FDA); or (b) approved by the Department").

[62] *See Clinical Laboratory Standards of Practice, General Systems Standards* (Effective May 5, 2021), DEP'T OF HEALTH, WADSWORTH CENTER, https://www.wadsworth.org/sites/default/files/WebDoc/EFFECTIVE_GeneralSystems_May2021_FINAL.pdf; *Laboratory Standards*, DEP'T OF HEALTH, WADSWORTH CENTER, https://www.wadsworth.org/regulatory/clep/clinical-labs/laboratory-standards (Specialty Requirements by Category).

[63] *See Test Approval, Making a Submission*, DEP'T OF HEALTH, WADSWORTH CENTER, https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval#Making%20a%20Submission (last visited Nov. 8, 2023).

[64] *See Assay Approval in Genetic Testing - Molecular*, DEP'T OF HEALTH, WADSWORTH CENTER, https://www.wadsworth.org/sites/default/files/WebDoc/Genetic_Testing_Molecular_Checklist_0713.pdf.

[65] *See Risk Attestation Form for Laboratory Developed Tests*, DEP'T OF HEALTH, WADSWORTH CENTER, https://www.wadsworth.org/sites/default/files/WebDoc/Risk_Attestation_Form_Nov_2023.pdf (last visited Nov. 8, 2023).

[66] Palmetto GBA, *Molecular Diagnostic Program (MolDX®) Coverage, Coding, and Pricing Standards and Requirements*, https://www.palmettogba.com/Palmetto/moldx.Nsf/files/MolDX_Manual.pdf/$File/MolDX_Manual.pdf?Open& (last visited Oct. 31, 2023).

information to demonstrate these standards and the requirements of the specific coverage determination are met, and those dossiers are reviewed by unbiased subject matter experts. The MolDX program has been adopted in 28 states and additional US territories, and according to MolDX, most molecular labs in the United States operate within its jurisdiction. MolDX reviews over 1,500 tests per year, and it has reviewed approximately 20,000 tests, a vast majority of which are LDTs, to date since the program was established in 2011.[67]

Private payers also have recognized the value of novel LDTs to provide quality health care. For example, one study analyzed coverage policies from the 19 largest U.S. private payers with publicly available policies and found that all payers covered certain noninvasive prenatal screening (NIPS) testing in high-risk singleton pregnancies based on robust clinical validity studies and modeled evidence of clinical utility, and eight of those payers also covered NIPS testing in average risk pregnancies, citing clinical validity studies and updated professional guidelines.[68]

Accordingly, it is simply false to refer to LDTs as unregulated, inadequately regulated, or unscrutinized. High-complexity laboratories are subject to multi-layered regulation, and individual LDTs are scrutinized by federal regulatory regimes (CLIA), state regulatory regimes (state clinical laboratory laws), accrediting organizations (e.g., CAP), proficiency testing entities, federal coverage programs, private payers, and individual clinicians in search of the best care for their patients.

III. FDA's Proposed Rule Fails to Recognize the Significant Contributions of LDTs to the Public Health.

As explained in the following subsections, FDA's characterization of LDTs in the Proposed Rule is misleading and ignores the significant contributions LDTs make to clinical care. Subsection (A) explains how LDTs have driven innovation in clinical care across therapeutic areas, and subsection (B) explains how LDTs are critical to meeting clinical care needs, including by improving access to testing. FDA's Proposed Rule and the RIA fail to consider the harms to public health of eliminating the LDT diagnostic innovation pipeline and removing life-saving tests from the market.

A. LDTs drive advances in the public health by innovating at the pace of science.

High-complexity laboratories that develop and perform LDTs have been responsible for some of the most cutting-edge and important innovations and breakthroughs in clinical care in our country. As explained further below, LDTs have pioneered new areas of science by (1) driving medical innovation and laying the groundwork for development of standardized test kits; (2) detecting and driving our public health response to emerging threats; and (3) supporting therapeutic product clinical trials. FDA's Proposed Rule and the RIA, fail to consider the harms to public health of eliminating LDTs that serve these important roles.

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[67] Palmetto GBA, *About Us*, https://www.dexzcodes.com/palmetto/dex.nsf/DID/FUVDWDSWOU (last visited Nov. 29, 2023).

[68] Andrew P. Dervan et al., *Payer Decision-Making for Next Generation Sequencing-Based Genetic Tests: Insights From Cell-Free DNA Prenatal Genetic Screening*, 19 GENETIC MED. 559 (2017), https://www.nature.com/articles/gim2016145.

1. LDTs have driven medical innovation and established new standards of care.

LDTs have been at the forefront of medical innovation for decades. In many cases, standard, routine FDA-cleared and -approved tests were first available only as LDTs in specialized laboratories.[69] In each case, LDTs were for many years the only available diagnostic tests for these conditions, and the analytical and clinical data generated by these LDTs later paved the way for clearance and approval of tests for similar intended uses.

BRCA1/BRCA2. The high rates of breast cancer mortality in women of certain families led to a decades-long search for the causes of inherent susceptibility to the disease. In February 1994, a team of researchers led by Mark Skolnick at Myriad Genetics, in conjunction with collaborators at the NIH, sequenced BRCA1 (BReast CAncer gene 1).[70] The laboratory began offering testing for hereditary breast and ovarian cancer susceptibility in 1996. Today, testing for BRCA1/BRCA2 mutations have become the standard of care for breast and ovarian cancer. Millions of women have been tested for mutations in these genes, which has led to better and earlier treatments and saved lives.

HSV Encephalitis. The WHO estimates that 3.7 billion people under age 50 (67%) globally have Herpes simplex virus (HSV) type 1 and another 491 million (13%) have HSV type 2.[71] HSV is the most common cause of fatal encephalitis worldwide.[72] Until the mid-1990s, the preferred method of diagnosing HSV infection was through an invasive brain biopsy procedure that carried a significant risk of morbidity.[73] Around 1995, however, laboratory scientists developed a polymerase chain reaction (PCR) test that performed equivalently to brain biopsy.[74] For nearly 20 years, the only method of PCR diagnosis for HSV encephalitis was an LDT. It was not until 2014 that FDA cleared a PCR test for diagnosis of the same.[75]

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[69] Karen L. Kaul et al., The Case for Laboratory Developed Procedures: Quality and Positive Impact on Patient Care, 4 ACAD. PATHOLOGY 1 (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5528950/.

[70] Yoshio Miki et al., *A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1*, 266 SCIENCE 66 (1994), https://courses.washington.edu/gs466/readings/miki.pdf. https://www.science.org/doi/10.1126/science.7545954?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.

[71] *Herpes Simplex Virus*, WORLD HEALTH ORG., (Apr. 5, 2023), https://www.who.int/news-room/fact-sheets/detail/herpes-simplex-virus.

[72] Elizabeth Matthews et al., *Herpesvirus-Associated Encephalitis: an Update*, 9 CURRENT TROPICAL MED. REP. 92 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9510386/.

[73] Kaul, *supra* note 69, at 3.

[74] *See, e.g.,* Fred D. Lakeman & Richard J. Whitley, *Diagnosis of Herpes Simplex Encephalitis: Application of Polymerase Chain Reaction to Cerebrospinal Fluid from Brain-Biopsied Patients and Correlation with Disease*, 171 J. INFECTIOUS DISEASE 857 (1995), https://academic.oup.com/jid/article-abstract/171/4/857/1032564.

[75] Kaul, *supra* note 69, at 3.

CMV. The CDC estimates that over half of adults have been infected with Cytomegalovirus (CMV) by age 40.[76] CMV is a form of herpes virus, and although a healthy person's immune system usually keeps the virus from causing illness, it can occasionally cause serious problems. It is one of the most common opportunistic infections following solid organ and hematopoietic stem cell transplant, and if left untreated and the virus invades certain tissues, it can cause liver, lung, heart, and bacterial infection and even death.[77] In the early 1990s, laboratory scientists developed a PCR test that could detect CMV infection in the plasma of transplant recipients.[78] LDTs were the sole method of diagnosing CMV until 2012.[79] During the intervening years, transplant physicians routinely used LDTs to screen asymptomatic patients in transplant centers and assess therapeutic treatment efficacy.[80]

KRAS Mutations. The KRAS gene (Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) is one of the most commonly mutated oncogenes in numerous cancers, such as non-small cell lung cancer, pancreatic ductal adenocarcinoma, and colorectal cancer.[81] Though cetuximab was lauded as a promising treatment for patients with colorectal cancer, a landmark 2006 study demonstrated that KRAS mutation is highly predictive of cetuximab resistance.[82] Molecular pathology laboratories developed LDTs to detect KRAS mutations, and KRAS mutational profiling quickly became the

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[76] *Cytomegalovirus (CMV) and Congenital CMV Infection*, CDC (Aug. 18, 2020), https://www.cdc.gov/cmv/index.html.

[77] *CMV and Transplant Patients*, CEDARS SINAI, https://www.cedars-sinai.org/health-library/diseases-and-conditions/c/cmv-and-transplant-patients.html (last visited Nov. 8, 2023).

[78] Dana G. Wolf & Stephen A. Spector, *Early Diagnosis of Human Cytomegalovirus Disease in Transplant Recipients by DNA Amplification in Plasma*, 56 TRANSPLANTATION 330 (1993), https://pubmed.ncbi.nlm.nih.gov/8395098/.

[79] *See* Raymond R. Razonable & Randall T.H. Hayden, *Clinical Utility of Viral Load in Management of Cytomegalovirus Infection After Solid Organ Transplantation*, 26 CLINICAL MICROBIOLOGY REV. 703 (2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3811235/.

[80] Kaul, *supra* note 69, at 5.

[81] Yunkai Yang et al., *KRAS Mutations in Solid Tumors: Characteristics, Current Therapeutic Strategy, and Potential Treatment Exploration*, 12 J. CLINICAL MED. 709 (2023), https://pubmed.ncbi.nlm.nih.gov/36675641/.

[82] *See* Astrid Lievre et al., *KRAS Mutation Status is Predictive of Response to Cetuximab Therapy in Colorectal Cancer*, 66 CANCER RESISTANCE 3992 (2006), https://aacrjournals.org/cancerres/article/66/8/3992/527155/KRAS-Mutation-Status-Is-Predictive-of-Response-to.

standard of care for patients with metastatic colon cancer.[83] It was not until 2014, however, that FDA approved a companion diagnostic to screen for KRAS mutations.[84]

NGS for oncology. In addition to the single-gene tests described above (BRCA1/2 and KRAS), LDTs have also driven the development of standard-of-care next generation sequencing (NGS) for oncology, more broadly. For example, current lung cancer guidelines recommend testing for over 10 tumor biomarkers at the time of diagnosis, and a study by Aggarwal, et al. shows that molecular genotyping before first line therapy is initiated leads to longer survival.[85] Although FDA began approving IVDs applying NGS technology for oncology applications starting in late 2016, the approved applications for such technology were initially narrow. And while such indications have since expanded, they are the result of more than a decade of development and refinement under the LDT framework.

There are numerous additional examples like these, where innovative LDTs have improved patient care for many years, even decades before there was an FDA-authorized standard kit. LDTs have long been a critical element of American medical innovation.

2. LDTs are a critical public health tool.

LDTs are essential for responding to public health threats in various forms, from emerging pathogens, to rare pathogens, to synthetic drugs. Their ability to be rapidly developed, validated, and performed makes them uniquely important to responding to emerging and constantly shifting public health needs. A few examples are demonstrative.

First, LDTs have always been at the forefront of providing access to testing for new and emerging pathogens, such as COVID-19, MPOX, Swine Flu, and Enterovirus D68, where FDA-cleared and -approved tests were not available until long after the need for testing arose. For COVID-19 in particular, LDTs were absolutely essential to the American public health emergency (PHE) response. As an initial matter, scientists relied on LDTs to diagnose COVID-19 even before the Secretary of HHS declared a PHE. For example, the first U.S. case of COVID-19 was diagnosed on January 20, 2020, using an unapproved assay developed and performed at the Centers for Disease Control and Prevention, i.e., a CDC LDT.[86] As explained further below in these comments, commercial LDTs were a vital component of the American response to the COVID-19 pandemic, and in contrast to the portrait painted by the Proposed Rule, FDA's policies ultimately recognized the importance—and quality—of these tests. Unfortunately, that recognition came approximately one

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[83] NAT'L COMPREHENSIVE CANCER NETWORK, PRACTICE GUIDELINES ESTABLISHED FOR KRAS MUTATION TESTING IN COLORECTAL CANCERS: NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES ON COLON AND RECTAL CANCERS (2008).

[84] Turna Ray, *With New Indication for Vecitibix, FDA Approves Qiagen's Therascreen KRAS Test as Companion Diagnostic*, GENOME WEB (May 28, 2014), https://www.genomeweb.com/clinical-genomics/new-indication-vectibix-fda-approves-qiagens-therascreen-kras-test-companion-dia.

[85] Charu Aggarwal et al., *Association Between Availability of Molecular Genotyping Results and Overall Survival in Patients with Advanced Nonsquamous Non-Small-Cell Lung Cancer*, 7 JCO PRECISION ONCOLOGY e2300191 (2023), https://pubmed.ncbi.nlm.nih.gov/37499192/.

[86] Michelle Holshue et al., *First Case of 2019 Novel Coronavirus in the United States*, 382 N ENGL. J MED. 929 (2020), https://www.nejm.org/doi/full/10.1056/nejmoa2001191.

month after the Agency's intervention prevented America's clinical laboratories from bringing LDTs to the public that would have facilitated contact tracing and allowed the pandemic to be more rapidly brought under control.[87]

More generally, a complex set of factors influence test developers' decisions to develop new diagnostic tests and ramp up manufacturing capacity and/or laboratory testing capacity in the face of an emerging pathogen.[88] However, these dynamics are less of a challenge for laboratories developing LDTs, and accordingly, laboratories are often the first developers taking action to develop tests in such circumstances.

Second, LDTs continue to be important for detecting rare and infectious pathogens where there is no FDA-cleared or -approved diagnostic available. For example, no FDA-approved tests were available to detect avian influenza virus, chikungunya virus, Ebola virus, Middle Eastern respiratory syndrome virus, severe acute respiratory syndrome virus, or Zika virus when those pathogens first emerged.[89] In the absence of FDA-cleared or -approved diagnostics, clinical laboratories developed, validated, and implemented LDTs that facilitated the rapid treatment and appropriate isolation of patients, thereby slowing the spread of potentially deadly infections.[90] In the immediate wake of infectious disease outbreaks, clinical laboratories play a vital role in rapidly diagnosing pathogens and decreasing overall mortality. LDTs are equally essential to the diagnosis of rare diseases. To this day, LDTs remain the only available diagnostics to detect the pathogen that causes high-risk human papilloma virus in oropharyngeal cancers and the genetic mutations that cause Huntington's Disease and epidermolysis bullosa.[91]

Third, LDTs are vitally important to our public health response to the evolving drug overdose epidemic, where novel psychoactive substances (NPS)—including benzodiazepines, fentanyls, and other opioids—are appearing and fading from the market faster than IVD test kits can be cleared or approved. This means that frequent and rapid modifications to tests are necessary to meet provider needs. One ACLA member laboratory reported validating new LDTs at least twice annually to keep

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[87] Barbara J. Evans and Ellen Wright Clayton, *Deadly Delay: The FDA's Role in America's COVID-Testing Debacle*, 130 YALE L. J., Forum (Jul. 29, 2020), https://www.yalelawjournal.org/forum/deadly-delay-the-fdas-role-in-americas-covid-testing-debacle (detailing the harm caused by FDA's policies that required emergency use authorizations for COVID-19 LDTs). The headlines from the early days of the pandemic, recounted in this article, are a jarring reminder: "How the Coronavirus Became an American Catastrophe"; "'Massive Blindspot': Missing Data in COVID Pandemic Leaves US Vulnerable"; "A Mayor Accepts a Nightmare: The COVID Tests Won't Come"; "'We're in Big Trouble': Microsoft Co-Founder Bill Gates Slams the 'Mismanagement' of the Coronavirus Testing System and Warns We Can't 'Wave a Wand' to Get the Economy Back to Normal"; and "It's Too Late to Avoid Disaster, but There Are Still Things We Can Do." *Id.*

[88] *See* Gigi Kwik Gronvall et al., *Proposal for a National Diagnostics Action Plan for the United States*, 5 HEALTH POL'Y OPEN 1 (2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10336495/.

[89] Kaul, *supra* note 69, at 6.

[90] *See, e.g.,* Victor Max Corman et al., *Performance and Clinical Validation of the RealStar MERS-CoV Kit for Detection of Middle East Respiratory Syndrome Coronavirus RNA*, 60 J. CLINICAL VIROLOGY 168 (2014), https://pubmed.ncbi.nlm.nih.gov/24726679/; Patrick Tang et al., *Interpretation of Diagnostic Laboratory Tests for Severe Acute Respiratory Syndrome: the Toronto Experience*, 170 CANADIAN MED. ASS'N J. 47 (2004), https://pubmed.ncbi.nlm.nih.gov/14707219/.

[91] Kaul, *supra* note 69, at 5, 12.

pace with new and emerging drugs, and that it added over 70 new analytes to its NPS LDTs in the last 14 months. Two ACLA member laboratories—Laboratory Corporation of America Holdings ("Labcorp") and Aegis Science Corporation ("Aegis") developed LDTs for detecting xylazine over a year before FDA issued its alert regarding xylazine in November 2022. FDA's alert acknowledged that "[r]outine toxicology screens do not detect xylazine, and additional analytical techniques are required to detect xylazine when it might be involved in illicit drug overdoses."[92] To date, over a year after FDA's alert, there are still no FDA-cleared or -approved xylazine IVD test kits, but ACLA member laboratories perform thousands of life-saving tests for xylazine every month using the LDTs they have developed. There also are no FDA-cleared or -approved test kits for many other NPS drugs, including many fentanyl analogues and designer drugs. Keeping pace with NPS requires deep expertise, ongoing investment, and rapid implementation of updates. Device law is simply inconsistent with these requirements, and FDA regulation of NPS LDTs would create a significant risk that the tests would fall behind, leading to major public health challenges.

3. LDTs advance therapeutic product development.

LDTs are also a vital component of therapeutic product development. Clinical trial assays (CTAs) are critical for collecting safety and effectiveness data about an investigational therapeutic product, and they are routinely developed as LDTs because no FDA-cleared or -approved assay is available. Moreover, because the assay cut-off may be adjusted over the course of product development (e.g., from early-phase (I/II) to late phase (III) clinical trial testing), therapeutic product sponsors frequently turn to high-complexity laboratories with the expertise and ability to nimbly validate modifications to the assay as needed. LDTs also are often developed for performance as CTAs to identify patients most likely to benefit from an investigational therapeutic product and may be the basis for a later cleared or approved companion diagnostic.

In many cases, LDTs developed for use as a CTA are available only to support drug development. For example, an ACLA member laboratory developed an LDT specifically for use in clinical trials of a then-investigational gene therapy product for treating hemophilia. The LDT measured endogenous factor VIII clotting protein developed by a patient *after* treatment with the gene therapy product, i.e., to measure the effectiveness of the gene therapy.[93] The therapeutic product has since been approved with a companion diagnostic offered by a different laboratory, but the CTA has not been commercialized.[94]

In other cases, drug developers partner with multiple laboratories to develop LDTs as CTAs to support enrollment of patients with rare diseases and conditions into a clinical trial. Partnership

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[92] *FDA Alerts Health Care Professionals of Risks to Patients Exposed to Xylazine in Illicit Drugs*, FDA (Nov. 8, 2022), https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-health-care-professionals-risks-patients-exposed-xylazine-illicit-drugs.

[93] *See* Christopher Tudan et al., *Development of a FVIII Antigen Assay to Quantify B-Domain Deleted FVIII Antigen in Human Plasma*, LABCORP.COM https://files.labcorp.com/labcorp-d8/BDD%20FVIII%20Ag_SSC_2018_Secure.pdf (last accessed Nov. 13, 2023). *See also* Steffen Rosen et al., *Activity of Transgene-Produced B-domain-Deleted Factor VIII in Human Plasma Following AAV5 Gene Therapy*, 136 BLOOD 2524 (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7714098/.

[94] *FDA Approves First Gene Therapy for Adults with Severe Hemophilia A*, FDA (June 29, 2023), https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-adults-severe-hemophilia.

with multiple laboratories is necessary because, due to the rarity of the disease or condition, many patients dispersed across the country need to be tested to identify enough trial participants to power the study appropriately.

B. LDTs are essential for meeting current clinical care needs.

LDTs are essential for meeting current clinical care needs because they are often the best available testing solution for patients. As discussed below, (1) many clinical tests are available *only* as LDTs either because no FDA-cleared or -approved test exists for a particular disease, condition, or patient population, or because patients do not have access to a cleared or approved IVD. In other cases, (2) even where an FDA-cleared or -approved test exists, an LDT for the same disease or condition performs better than the cleared or approved test, and has accordingly become the standard of care. The Proposed Rule would cause many of these tests to be withdrawn from the market. However, the Proposed Rule and the RIA failed to consider how withdrawal of these life-saving assays would harm the public health.

1. LDTs are often the only available tests for patients.

In many cases, LDTs are the only available testing solution for patients because there is no approved or cleared test for a particular disease or condition, or the approved or cleared test is inaccessible to the patient. LDTs have been developed to address unmet clinical needs for patients, and approved or cleared IVDs have been modified as LDTs to increase access to testing for patients.

First, there are many diseases and conditions for which there is no approved or cleared IVD, and in these cases, the patients' options are to receive a diagnosis supported by results from an LDT, or no *in vitro* diagnostic information at all. For example, the only tests available to help diagnose Rett Syndrome—one of the most common genetic causes of developmental and intellectual impairment in girls[95], Fabry Disease—a rare and progressive lysosomal storage disorder[96], and UBE3A mutation in patients with Angelman's Syndrome—a rare neuro-genetic disorder that causes developmental delays[97] are available as novel LDTs. There are no FDA-cleared or -approved alternatives for these patients. Given the economics of commercial test development, rare diseases frequently lack a commercialized, FDA-cleared or -approved test. Laboratories have filled this gap by developing tests for a very small group of people, thereby meeting unmet clinical needs.[98]

Second, even when an approved or cleared IVD exists, it may not be available or accessible to a patient for a variety of reasons (e.g., no local laboratory with instrumentation compatible with the cleared or approved test kit; insufficient testing capacity at local laboratories using the cleared/approved test kit). In these cases, laboratories may modify existing IVD test kits to use the

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[95] Cary Fu et al., CONSENSUS GUIDELINES ON MANAGING RETT SYNDROME ACROSS THE LIFESPAN, 4 BMJ PAEDIATRICS OPEN (2020), https://bmjpaedsopen.bmj.com/content/4/1/e000717.

[96] Sanofi Genzyme, *Testing Options for Fabry Disease*, DISCOVER FABRY (2020), https://www.discoverfabry.com/dam/jcr:2ba6f274-1f1d-43aa-84e6-3b1411258536/Testing%20Options%20for%20Fabry%20Disease%20%20SAUSFD17041244g2.pdf.

[97] NIH, *Angelman Syndrome*, GENETIC TESTING REGISTRY, https://www.ncbi.nlm.nih.gov/gtr/conditions/C0162635/ (last visited Nov. 13, 2023).

[98] Christina Cifaldi et al., *Targeted NGS Platforms for Genetic Screening and Gene Discovery in Primary Immunodeficiencies*, 10 FRONTIERS OF IMMUNOLOGY 1 (2019), https://pubmed.ncbi.nlm.nih.gov/31031743/.

laboratory's instrumentation, increase testing capacity by leveraging high-throughput instrumentation, or extending specimen stability to allow samples to be received from more remote locations.

For example, the BD Multitest™ 6-color TBNK Reagent is a cleared flow cytometry reagent intended for use to identify and determine the percentages and absolute counts of T, B, and natural killer (NK) cells, as well as the CD4 and CD8 subpopulations of T cells in peripheral blood.[99] According to the 510(k) decision summary, specimens must be stained within 24 hours of blood draw.[100] However, many patients do not live within close enough proximity to a laboratory with flow cytometry testing capability for their sample to be tested locally. Instead, their specimen needs to be sent to a reference laboratory, which could take more than 24 hours. Accordingly, one ACLA member that operates a high-complexity reference laboratory has performed extended stability studies to validate testing on specimens stained within 48 hours of collection, thereby expanding access to this test for patients who cannot be served by a local laboratory.

As another example, the KRONUS Zinc Transporter 8 Autoantibody (ZnT8Ab) ELISA Assay is intended for the semi-quantitative determination of autoantibodies to Zinc Transporter 8 (ZnT8) in human serum, and may be useful as an aid in the diagnosis of Type 1 diabetes mellitus.[101] According to the instructions for use, "[s]era to be analyzed should be assayed soon after separation or stored … at or below -20°C."[102] However, once again, many patients do not live within close enough proximity to a laboratory that performs this assay such that the specimen can be analyzed immediately, and storage of specimens "at or below -20°C" is not always possible. Accordingly, one ACLA member has validated specimen stability for this assay at room temperature and for an increased amount of time between collection and analysis, thereby extending the stability specifications for the assay when performed in its high-complexity laboratory.

These types of modifications to the cleared or approved test kit transform the testing service to performance of an LDT. Virtually all reference laboratories depend on this flexibility to meet the needs of their patients. However, under the Proposed Rule, many of these modifications would not be made because the requirement for obtaining an FDA marketing authorization would create too large of a barrier.

Third, even when a cleared or approved IVD exists, the scope of the clearance may not be adequate to reach an important patient population. Accordingly, LDTs are an essential tool for improving access to testing for underserved patient populations. For example, the Aptima Combo 2® Assay is intended to aid in the diagnosis of chlamydial and/or gonococcal urogenital disease

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[99] 510(k) Summary for K090967, BD Multitest™ 6-color TBNK Reagent (July 31, 2009) https://www.accessdata.fda.gov/cdrh_docs/pdf9/K090967.pdf.

[100] 510(k) Decision Summary for K090967, BD Multitest™ 6-color TBNK Reagent, https://www.accessdata.fda.gov/cdrh_docs/reviews/K090967.pdf (last visited Nov. 13, 2023).

[101] De Novo Decision Summary for DEN140001, KRONUS Zinc Transporter 8 Autoantibody (ZnT8Ab) ELISA Assay, https://www.accessdata.fda.gov/cdrh_docs/reviews/den140001.pdf (last visited Nov. 13, 2023)

[102] KRONUS, ZincTransporter 8 Autoantibody (ZnT8Ab) ELISA Assay Package Insert (Aug. 2022).

using the PANTHER System.[103] According to the instructions for use, "[t]he performance of the AC2 assay has not been evaluated in adolescents less than 14 years of age."[104] However, there are patients less than 14 years of age that need to be tested, including to support investigations into potential cases of sexual abuse. Accordingly, one ACLA member has validated this test system for use in patients less than 14 years of age. As another example, and as discussed further below, although some cleared/approved newborn screening tests exist, hospitals frequently rely on LDTs because the list of diseases for which newborns are screened far exceeds the cleared indications for IVD kits.[105] The Proposed Rule's most likely effect, however, would be to deprive patients access to these life-saving tests.

2. LDTs perform better than cleared or approved tests.

LDTs are also important to meet current clinical needs because, in many cases, they perform better than, and are preferred by clinicians over, cleared or approved alternatives. This often happens when the technology underlying a cleared or approved test has become outdated, the scope of the cleared or approved test is too narrow, or the cleared or approved test is associated with poor performance. In these cases, an LDT that uses modern, improved technology, performs with greater analytical validity, and can be used to support greater clinical care rapidly becomes the standard of care with nearly uniform preference among clinicians.

For example, there are some cleared/approved IVDs for newborn screening, but these test kits screen for a limited number of diseases and conditions, and do not include most genetic disorders. Rapid whole genome sequencing (rWGS), on the other hand, is a genetic testing method that can diagnose any one of *thousands* of Mendelian disorders in seven days or less.[106] The incredible power of rWGS is that it allows for a clinician to order a single test and obtain genetic information to inform a diagnosis in an incredibly rapid manner, even when there is a constellation of clinical findings present in the patient. One study reported that for acutely ill newborns, rWGS generated a diagnosis within a median time of 3 days for 40% of patients, and led to a change in medical care for 32% of patients.[107] rWGS is by far the most comprehensive genetic screening tool

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[103] 510(k) Summary for K111409, APTIMA Combo 2® Assay (May 3, 2012), https://www.accessdata.fda.gov/cdrh_docs/pdf11/K111409.pdf; 510(k) Summary for K132251 for APTIMA Combo2 2® Assay (Oct. 17, 2013), https://www.accessdata.fda.gov/cdrh_docs/pdf13/K132251.pdf.

[104] Hologic, Aptima Combo 2® Assay (Panther® System), Package Insert (Valid Date: From: 2023-07), https://www.hologic.com/package-inserts/diagnostic-products/aptima-combo-2-assay-ctng (last visited Nov. 4, 2023).

[105] *Compare* North Carolina Department of Health and Human Services, Newborn Screening: NC Newborn Screening Program Panel, https://slph.dph.ncdhhs.gov/newborn/DisordersTested.asp (last visited Nov. 7, 2023) *and* 510(k) Decision Summary for K193103 (NeoBase 2 Non-derivatized MSMS Kit), https://www.accessdata.fda.gov/cdrh_docs/reviews/K193103.pdf (last visited Nov. 13, 2023).

[106] *See, e.g.*, ARUP Laboratories, *Whole Genome Sequencing*, https://ltd.aruplab.com/api/ltd/pdf/204 (last visited Nov. 13, 2023).

[107] David Dimmock et al., *Project Baby Bear: Rapid Precision Care Incorporating rWGS in 5 California Children's Hospitals Demonstrates Improved Clinical Outcomes and Reduced Costs of Care*, 108 AM. J. HUM. GENETICS 1231 (2021), https://pubmed.ncbi.nlm.nih.gov/34089648/.

available, and as such has quickly become the standard of care genetic test for patients in need of rapid diagnosis. There currently are no FDA-cleared or -approved rWGS tests.

Mass spectrometry tests for detecting hormones, drugs, and proteins are another important example of how laboratory science rapidly eclipses FDA-cleared and -approved tests. Mass spectrometry methods offer analytical advantages over conventional immunoassay-based approaches,[108] but even FDA has acknowledged that "[m]ass spectrometry-based *in vitro* diagnostic devices that measure proteins and peptides are underutilized in clinical practice."[109] Many clinical practice guidelines recommend the use of mass spectrometry-based tests for clinical management of hormone disorders such as congenital adrenal hyperplasia,[110] Cushings Syndrome,[111] late-onset hypogonadism in males,[112] and polycystic ovary syndrome,[113] as well as generally for the measurement of testosterone.[114] Other mass spectrometry -based clinical proteomic LDTs have been developed to measure proteins with functions related to endocrinology, microbiology, cancer, and Alzheimer's disease.[115]

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[108] Paul J Jannetto & Robert L Fitzgerald, *Effective Use of Mass Spectrometry in the Clinical Laboratory*, 62 CLINICAL CHEMISTRY 92 (2016), https://academic.oup.com/clinchem/article/62/1/92/5611766?login=true. *See also* Judith A. Stone & J Grace van der Gugten, *Quantitative Tandem Mass Spectrometry in the Clinical Laboratory: Regulation and Opportunity for Validation of Laboratory Developed Tests*, 28 J. MASS SPECTROMETRY & ADVANCES IN THE CLINICAL LAB. 82 (2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10017411/.

[109] Julia Tait Lathrop et al., *US Food and Drug Administration Perspectives on Clinical Mass Spectrometry*, 62 CLINICAL CHEMISTRY 41 (2016), https://academic.oup.com/clinchem/article/62/1/41/5611809?login=true. *See also* Judith A. Stone & J Grace van der Gugten, *supra* note 108, at 82–90 ("While LC-MSMS offers advantages over more traditional IA-based laboratory techniques, LDTs are a necessity for implementation of clinical LC-MSMS tests. Manufacturers of LC-MSMS platforms do not typically supply FDA-approved tests….").

[110] Phyllis W Speiser et al., *Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline*, 103 J. CLINICAL ENDOCRINOLOGY & METABOLISM 1 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6456929/.

[111] Lynnette K Nieman et al., *The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline*, 93 J. CLINICAL ENDOCRINOLOGY & METABOLISM 1526 (2008), https://academic.oup.com/jcem/article/93/5/1526/2598096.

[112] Christina Wang et al., *Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations*, 30 J. ANDROLOGY 1 (2009).

[113] Helena J Teede et al., *Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome*, 108 J. CLINICAL ENDOCRINOLOGY & METABOLISM 10 (2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10505534/.

[114] William Rosne et al., *Position Statement: Utility, Limitations, and Pitfalls in Measuring Testosterone: An Endocrine Society Position Statement*, 92 J. CLINICAL ENDOCRINOLOGY & METABOLISM 405 (2006), https://academic.oup.com/jcem/article/92/2/405/2566757?login=true.

[115] Yanchun Lin & Stefani N Thomas, *Impact of VALID Act Implementation on Mass Spectrometry-Based Clinical Proteomic Laboratory Developed Tests*, 28 J. MASS SPECTROMETRY & ADVANCES IN THE CLINICAL LAB. 28, 32 (Table 1) (2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9971545/.

Another important example is antimicrobial susceptibility testing (AST), where FDA-cleared and -approved tests do not meet modern performance standards. Currently, FDA approves specific drug/organism combinations used in cleared automated testing instruments, but those specific combinations quickly become outdated as organisms rapidly change their susceptibility over time by acquiring resistance to antimicrobials. Accordingly, international organizations such as the Clinical and Laboratory Standards Institute (CLSI) provide updated recommendations on what drug levels determine resistance for a particular organism, but manufacturers cannot adjust to these updated recommendations without obtaining additional FDA clearance.[116] The result is that many previously FDA-cleared AST panels are inaccurate, providing clinically wrong information on which drugs are most likely to be effective at treating a particular infection. Rather than provide such inaccurate information, many laboratories report out more accurate information using LDTs. A similar issue exists for test kits with listed interfering substances. As new therapies are introduced, there are new possibilities of interfering substances impacting certain test results. Rather than accepting the possibility that test results could be negatively impacted, laboratories often validate procedures to account for these new interfering substances using LDTs.

Finally, some FDA-cleared and -approved tests do not even meet modern CLIA and CAP performance standards. For example, FDA cleared a hematology analyzer with several % CV values for leukocytes (white blood cells) above 10% and two % CV values for body fluid red blood cells above 4%,[117] failing the criteria for acceptable performance under the new CLIA proficiency testing rules.[118] As another example, CAP requires specimen stability studies for all LDTs,[119] but FDA has authorized some IVDs without data to support test-specific specimen stability.[120]

FDA's Proposed Rule fails to consider the impact that would result from FDA regulation related to these issues. FDA must consider the increased costs that would be associated with these categories of tests, such as the cost of continually updating ASTs, the costs of obtaining and sustaining approvals for virtually all mass spectrometry tests – or the costs to patients and our health care system if those tests are withdrawn by laboratories or cannot be updated in a timely manner as a result of FDA regulation.

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[116] Andrea Prinzi, *Updating Breakpoints in Antimicrobial Susceptibility Testing*, AM. SOC'Y MICROBIOLOGY (Feb. 22, 2022), https://asm.org/Articles/2022/February/Updating-Breakpoints-in-Antimicrobial-Susceptibili.

[117] Decision Summary for K162977, https://www.accessdata.fda.gov/cdrh_docs/reviews/K162977.pdf (last visited Nov. 13, 2023).

[118] Final Rule, *Clinical Laboratory Improvement Amendments of 1988 (CLIA) Proficiency Testing Regulations Related to Analytes and Acceptable Performance*, 87 Fed. Reg. 41194 (Aug. 10, 2022) (amending 42 CFR 493.941, effective July 11, 2024).

[119] *See* COLL. AM. PATHOLOGISTS, *supra* note 55, at at COM.40350 (Validation of Test Performance Specifications – Modified FDA-cleared/approved Tests and LDTs).

[120] *See, e.g.*, Instructions for Use for Roche cobas® ALB2, Albumin Gen.2 (2013-10, V 4.0 English) (citing as support for stability specifications, "WHO Publication: Use of antiocoagulants in diagnostic laboratory investigations, WHO/DIL/LAB/99.1 Rev.2:Jan 2002"); Instructions for Use for Inova Diagnostics QUANTA lite® ASCA IgG ELISA (*S. cerevisiae*) (October 2015 Revision 8) (relying on NCCLS Document H18-A2 recommendations for sample stability specifications).

IV. FDA's Characterization of LDTs is Inaccurate.

FDA's assertion that the Proposed Rule is necessary is based on a flawed characterization of LDTs, and ACLA strongly disagrees with FDA's characterization of LDTs as "problematic." As explained in the following subsections: (A) FDA's methodology for critiquing LDTs is fundamentally flawed because rather than systematically reviewing available evidence, FDA relies on anecdotes and unproven complaints, and it does not establish a baseline for comparison; and (B) FDA's critiques of specific LDTs or categories of LDTs are misguided. This faulty "evidence" cannot be the basis for any proposed policy regarding LDTs.

A. FDA's methodology for critiquing LDTs is flawed.

FDA is proposing to initiate sweeping regulation of LDTs on the basis of flimsy and inaccurate data. The Proposed Rule points to four main sources of evidence: (1) literature; (2) allegations/reports to FDA; (3) FDA's experience reviewing submissions; and (4) news stories. However, all of this "evidence" is anecdotal and/or unverified, and FDA would never accept this type of "evidence" from any regulated entity as the basis for a regulatory decision. FDA cannot finalize the Proposed Rule based on anecdotes, especially when it has the tools to systematically collect the information it needs to make informed policy decisions.

First, FDA selectively shares information about LDTs that it asserts are "problematic," but it makes no attempt to contextualize such examples within the very large market of available LDTs and the decades of reliance on such tests.[121] For example, FDA estimates that 1,200 high-complexity laboratories offer a total of 80,400 LDTs, but publicly available information suggests this number is higher. For example, considering that only 200 U.S. laboratories were reportedly offering 37,124 *genetic* tests for clinical purposes in November 2022, 80,400 LDTs is likely a significant underestimate of all available LDTs today.[122]

Even if FDA were correct to be concerned about the identified LDTs (it is not), those LDTs would represent only a tiny fraction of a percent of LDTs being performed today, or ever. Based on our count in reviewing the Proposed Rule and the cited references, FDA appears to have identified approximately 160 LDTs that it implies are unreliable or otherwise problematic. However, even using FDA's estimate of 80,400 available LDTs, FDA's anecdotal references reflect only ~0.2% of available LDTs. Stated differently, FDA has offered no evidence of harm with respect to 99.8% of currently available LDTs. FDA also makes no attempt to contextualize its concerns in the decades of reliance on LDTs, during which time likely billions of LDTs have been performed to inform patient care. Instead, FDA acknowledges that it has not "systematically collect[ed] information" on LDTs,

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[121] Indeed, at several points within the preamble to the Proposed Rule, FDA expressly acknowledges that its evidence is "anecdotal." *See* 88 Fed. Reg. at 68010 ("As the testing landscape as evolved, information about these tests in the scientific literature, news articles, and **anecdotal reports** submitted to the Agency, among other sources, has exposed evidence of problems associated with these tests.") and 86012 ("As noted above, collectively, this information, **though anecdotal**, points to **potential problems** among IVDs offered as LDTs….").

[122] Alyssa L. Halbisen & Christine Y. Lu, T*rends in Availability of Genetic Tests in the United States, 2012–2022*, 13 J. PERSONALIZED MED. 638 (2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10142561/.

proposes to apply its device authorities to such tests "[b]ased on current safety signals," and points to "limitations in the data" as justification for extrapolating evidence in its cost-benefit analysis.[123]

Second, many of FDA's sources of "evidence" are unverified, and it is inappropriate to base this sweeping regulatory action on unsubstantiated anecdotes and conjecture. For example, FDA states that it has "received multiple complaints, adverse events reports, and other allegations identifying problems with IVDs offered as LDTs," but then immediately admits in a footnote that "FDA has not confirmed the veracity of the allegations or facts in every complaint report, and allegation."[124] FDA likewise points to legal complaints filed by consumers, shareholders, litigants, and investors, but these complaints—by definition—are based on unproven facts. If LDTs actually performed poorly, treating physicians would stop using them and would call attention to the medical community regarding the bad test experience. But this is not the case: physicians continue to rely on LDTs every day to inform patient care.

Third, even if FDA's stated concerns with LDTs were verified, the Agency has not demonstrated that these concerns would be addressed by FDA regulation. This is a recurring issue with FDA assertions that it must regulate LDTs to protect the public health. Indeed, following FDA's 2015 memo citing 20 case studies of LDTs that it claimed constituted "public health evidence for FDA oversight of laboratory developed tests," an analysis authored by the Association for Molecular Pathology (AMP) demonstrated that the harms identified by FDA were largely fictional and few would actually be addressed by FDA regulation.[125] And FDA's current assertions that it must regulate LDTs to protect the public health are similarly unjustified because the Agency has offered no comparison to the prevalence of these concerns with cleared and approved IVDs. FDA has not demonstrated that LDTs present any greater risk than cleared and approved IVDs.

FDA raises concerns that LDTs sometimes yield inaccurate results, but cleared and approved IVDs also yield inaccurate results. Cleared and approved IVDs do not have perfect analytical or clinical validity. In fact, every test has a certain sensitivity and specificity, reflecting that false positives and false negatives are possible. Depending on a variety of factors, the sensitivity and specificity of tests may be relatively high, but in other cases, the sensitivity and specificity may be lower. For example, in 2022, a novel kidney test was classified through the De Novo pathway with sensitivity ranging from 76% to 93% and specificity ranging from 45% to 51%, and with precision/reproducibility studies generating high coefficients of variation across sites and lots (9.1% to 18.3%).[126] Notwithstanding that level of accuracy, FDA concluded that the value of having this tool available to clinicians outweighed the potential for false negative and false positive results. But applying the same reasoning that FDA applies to LDTs, the fact that this test has inaccurate results would render this test "problematic."

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[123] 88 Fed. Reg. at 68008, 68010.

[124] *Id.* at 68011.

[125] AMP, *Facts FDA Ignored: An analysis of the FDA report, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies"* (Dec. 13, 2015), https://www.amp.org/AMP/assets/File/position-statements/2015/AMPResponseFDACaseReportFinal.pdf?pass=54.

[126] *See, e.g.*, Decision Summary for DEN130031 (NEPHROCHECK® Test system), https://www.accessdata.fda.gov/cdrh_docs/reviews/den130031.pdf (last visited Nov. 8, 2023).

FDA also receives reports and allegations regarding poor performance of cleared and approved IVDs. FDA's own Manufacturer and User Facility Device Experience (MAUDE) database includes many complaints associated with various approved or cleared IVDs. Furthermore, there have been many recalls of FDA-cleared or -approved diagnostics for quality or other issues that impact the accuracy of those tests. In short, FDA regulation is not a panacea, and the claims embedded in the Proposed Rule vastly overstate the claimed benefits of subjecting LDTs to the burdens of FDA regulation.

FDA's proposal to apply device authorities to LDTs on the basis of anecdotal and unproven evidence without comparison to available evidence for IVDs is hypocritical of an agency that demands much more from the entities it regulates. The Agency demands that device applications are supported by systematically collected "valid scientific evidence,"[127] and accepts real world evidence only when the underlying data meets this threshold.[128] The Agency should not be proposing sweeping policy changes on the basis of anything less. In fact, FDA's own regulation provides that "[i]solated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence,"[129] which is exactly the type of evidence that FDA is relying upon to justify this vast expansion of its regulatory reach.

B. FDA's specific critiques are inaccurate.

It is not possible, nor necessary, to respond to every allegation that FDA makes in its Proposed Rule in this compressed comment period.[130] Nonetheless, it is imperative to correct the record with regard to certain categories of tests that FDA has broadly characterized as problematic. In particular, ACLA was disappointed with how FDA mischaracterized the quality, validity, and importance of LDTs for COVID-19, NIPS, and oncology. FDA cannot finalize the Proposed Rule based on its mischaracterization of these tests.

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[127] *See* 21 CFR § 860.7(c)(1)-(2) ("[T]he agency relies only on valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective.") & ("Valid scientific evidence is evidence from well-controlled clinical investigations, partially controlled studies, studies and objective trials with matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.").

[128] FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: USE OF REAL-WORLD EVIDENCE TO SUPPORT REGULATORY DECISION-MAKING FOR MEDICAL DEVICES (2017), https://www.fda.gov/media/99447/download.

[129] *See* 21 CFR § 860.7(c)(2).

[130] ACLA remains disappointed that the Agency rejected multiple requests to extend the comment period beyond 60 days, even while the Agency took at least seven months to develop its proposed rule. *See* Mark McCarty, *Hillebrenner Says FDA No Longer Waiting on Congress for LDT Regulation*, BIOWORLD.COM (Mar. 1, 2023), https://www.bioworld.com/articles/694701-hillebrenner-says-fda-no-longer-waiting-on-congress-for-ldt-regulation?v=preview (announcing FDA's intentions to proceed with rulemaking as early as March 1, 2023).

1. FDA's characterization of COVID-19 LDTs is inaccurate.

FDA's characterization of COVID-19 LDTs is both incomplete and inaccurate. FDA completely ignores that LDTs were critical to the American response to the PHE, and instead draws inaccurate conclusions that threaten to erode the public's trust in clinical laboratories. As an initial matter, the first confirmed case of COVID-19 in the United States was diagnosed by an LDT, even before the PHE was formally declared. And as the pandemic evolved, LDTs continued to be a source of reliable testing.

Specifically, once the PHE was declared, LDTs were among the *first* reliable testing options available to Americans because test kits were not available. Although FDA granted an EUA for the CDC SARS-CoV-2 molecular diagnostic test kit, the test kit could not be validated by other laboratories and was unusable for weeks.[131] By relying only on IVDs for COVID testing, American testing capacity lagged far behind that of other countries.[132] It was only after FDA issued a more flexible policy to allow laboratories developing LDTs to step in that testing capacity for Americans soared. Within two and a half months of issuing the policy, 245 laboratories had notified FDA that they would begin testing.[133]

FDA's characterization of COVID-19 LDTs in the preamble to the Proposed Rule is also based on anecdotal evidence that is improperly extrapolated without context. For example, FDA points to the first 125 COVID-19 LDT EUA submissions as proof that laboratories do not perform appropriate or adequate validation studies.[134] The Agency claims that 82 of these submissions "showed test

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[131] The problems with the CDC test are well documented. *See, e.g.*, Shawn Boburg et al., *Inside the Coronavirus Testing Failure: Alarm and Dismay Among the Scientists Who Sought to Help*, WASH. POST (April 5, 2020); SUZANNE MURRIN, HHS OFFICE OF THE INSPECTOR GENERAL, FDA REPEATEDLY ADAPTED EMERGENCY USE AUTHORIZATION POLICIES TO ADDRESS THE NEED FOR COVID-19 TESTING (2022), https://oig.hhs.gov/oei/reports/OEI-01-20-00380.pdf ("CDC's first test was unusable for many weeks while no other test was authorized.").

[132] Shawn Boburg, et al., *supra* note 131 (Whereas the United States had performed a total of 2,009 tests by February 12, "[i]n South Korea, 1,000 people were being tested each day by mid-February, a number that would increase more than tenfold by the end of the month. The Geneva-based World Health Organization, meanwhile, had already delivered 250,000 diagnostic tests designed and manufactured by a German lab to 70 laboratories around the world."). *See also*, Barbara J. Evans and Ellen Wright Clayton, *supra* note 87.

[133] SUZANNE MURRIN, *supra* note 131. Indeed, FDA's evolving COVID-19 Testing Policy recognized the accuracy and reliability of LDTs compared to IVD test kits. At one point, FDA modified its testing policy to extend to LDTs and IVDs for COVID-19 serology tests, but then retracted this policy with regard to test kits after discovering that several of the commercially manufactured tests were unreliable. FDA, GUIDANCE FOR INDUSTRY: POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY 7 (2020) ("FDA has become aware that a concerning number of commercial serology tests are being promoted inappropriately, including for diagnostic use, or are performing poorly based on an independent evaluation by the NIH, indicating that greater FDA oversight of commercial serology tests is important to protect the public health.") (citations and footnotes omitted). While laboratories could still introduce serology tests without EUA authorization, kit manufacturers could not. The distinction FDA drew in its own policy was clear: without FDA oversight, commercial manufacturers did not produce reliable tests; but CLIA oversight of laboratories ensured the quality of LDTs.

[134] 88 Fed. Reg. 68011.

design or validation problems," but fails to acknowledge that many of these supposed problems were a direct result of incomplete and constantly changing guidance from FDA, as well as the realities of responding in real-time to a public health emergency where laboratories were doing all they could to expand the testing capacity of the country.

In particular, in FDA's memorandum detailing this assessment of the first 125 COVID-19 LDT EUA submissions, the Agency asserts that issues with validation included that "laboratories did not provide minimal descriptive information about their validation studies in the EUA request for FDA to assess the performance."[135] However, failure to provide this descriptive information does not affect—at all—the quality of the validation studies themselves. Rather, failure to provide this information reflects that laboratories, accustomed to validating tests pursuant to CLIA, CAP, New York State requirements, and other industry standards, did not have clear or consistent direction from FDA regarding which information to provide in an EUA request.

As another example from the memorandum, FDA asserts that "[t]he most common issue with analytical validation was related to use of synthetic DNA or small fragments of synthetic RNA," rather than viral RNA, but then immediately admits that "viral RNA was difficult to obtain through April 2020, and so FDA had recommended," but did not require, "that if synthetic RNA was used, validation should include full length or long strand RNA to closely approximate natural viral RNA."[136] FDA also acknowledged that "alternative approaches, such as creating contrived specimens with synthetic DNA, can be used, particularly in the early stages of an emergency when availability of viral RNA is limited."[137] It is wrong to portray clinical laboratories as being unable to perform appropriate or adequate validation studies when such studies were performed based on FDA guidance and the best available materials in the midst of a global pandemic.

It is also wrong to suggest that FDA's dissatisfaction with the quality of EUA submissions directly translated to bad tests, particularly when "[i]n the majority of cases, the FDA worked with the laboratories to correct the issues and permit continued testing."[138] Indeed, in a similar context—EUAs for MPOX diagnostics—a published report details how FDA's requests for additional validation studies or data did not meaningfully affect test performance and offered minimal benefits.[139] Laboratories report similar experiences with COVID-19 diagnostics.

Finally, it is wrong to suggest that the identified challenges with test design and validation were unique to laboratories. Rather, as FDA acknowledged, "[s]imilar problems were seen with commercial manufacturers" at the time.[140] And, contrary to the implication that LDTs perform worse than test kits, at least one study found 100% agreement between certain commercial and laboratory

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[135] ELIZABETH HILLEBRENNER, ASSOCIATE DIRECTOR FOR SCIENTIFIC AND REGULATORY PROGRAMS, CDRH, FDA, MEMORANDUM: SUMMARY OF 2020 ASSESSMENT OF THE FIRST 125 EUA REQUESTS FROM LABORATORIES FOR MOLECULAR DIAGNOSTIC TESTS FOR SARS-COV-2 (Sept. 22, 2023).

[136] *Id.*

[137] *Id.*

[138] Jeffrey Shuren & Timothy Stenzel, *Covid-19 Molecular Diagnostic Testing—Lessons Learned*, 383:e97 N. ENG. J. MED. (2020), *https://doi.org/10.1056/nejmp2023830*.

[139] Caldera, *supra* note 10. .

[140] SHUREN AND STENZEL, *supra* note 138.

tests for SARS-CoV-2.[141] Moreover, throughout the public health emergency, there were reported accuracy and quality concerns with EUA-authorized test kits.[142]

Other evidence cited by FDA also cannot reasonably be construed to suggest that CLIA-certified, high-complexity clinical laboratories systematically produced bad COVID-19 tests. For example, FDA cites a *ProPublica* report on a COVID-19 test offered by a laboratory in Chicago that missed 96 percent of positive cases,[143] but that laboratory had so many CLIA deficiencies that a CMS report concluded the public was put in "immediate jeopardy" by the laboratory's operation.[144] Accordingly, the poor performance of this laboratory's COVID-19 LDT is not indicative of the performance of LDTs developed by high-complexity laboratories that are operating in compliance with CLIA.

2. FDA's characterization of non-invasive prenatal screening (NIPS) is inaccurate.

NIPS is widely viewed as a breakthrough in prenatal care, but FDA's characterization of these tests reflects a fundamental misunderstanding of their intended use and their role in prenatal care. First, FDA's preamble distorts the difference between screening and diagnostic testing – a basic tenet of laboratory medicine. NIPS analyzes cell-free DNA that is naturally shed by the placenta cells into the pregnant patient's blood. NIPS tests are screening tests: they are intended to assess whether a pregnant patient may be carrying a fetus at increased risk of having a genetic disorder. Accordingly, a "positive" NIPS result indicates that the fetus is at higher risk of having a genetic disorder, but it is not a diagnosis. To obtain a firm diagnosis, further diagnostic testing should be used. However, a "negative" diagnostic test result does not mean that the "positive" NIPS result was wrong or a "false

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[141] Kerry Dust et al., *Comparison of Commercial Assays and Laboratory Developed Tests for Detection of SARS-CoV-2* (2020), 285 J. VIROLOGICAL METHODS 113970 (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7482591/ (comparing the performance of two commercial assays, the cobas® SARS-CoV-2 (Roche Diagnostics) and Xpert® Xpress SARS-CoV-2 (Cepheid®) tests, and a laboratory developed RT-PCR test adapted for use on the Hologic® Panther Fusion® (Hologic®) instrument as well as Bio-Rad and QIAGEN real-time PCR detection systems).

[142] *See, e.g.*, FDA, *Potential for False Positive Results with Certain Lots of Ellume COVID-19 Home Tests Due to a Manufacturing Issue: FDA Safety Communication* (Oct. 5, 2021) https://www.fda.gov/medical-devices/safety-communications/potential-false-positive-results-certain-lots-ellume-covid-19-home-tests-due-manufacturing-issue-fda#Actions (class I recall affecting around 2 million tests); FDA, *Do Not Use Certain SD Biosensor Pilot COVID-19 At-Home Tests: FDA Safety Communication* (May 4, 2023), https://www.fda.gov/medical-devices/safety-communications/do-not-use-certain-sd-biosensor-pilot-covid-19-home-tests-fda-safety-communication (class I recall affecting over 500,000 tests).

[143] 88 Fed. Reg. at 68012 (citing Anjeanette Damon, *The COVID Testing Company That Missed 96% of Cases*, PROPUBLICA (May 16, 2022), https://www.propublica.org/article/covid-testing-nevada-false-negatives-northshore).

[144] *See* CMS, *Survey of Northshore Clinical Laboratories, Inc.* (Dec. 29, 2021), https://s3.documentcloud.org/documents/21872905/northshore-clinical-labs-14d0426602-form-cms-2567-12292021.pdf.

positive."[145] As an analogy, a mammogram indicating risk of breast cancer is not "wrong" just because a biopsy or other follow-up testing reveals that the patient does not have breast cancer. The mammogram did its job: it selected a subset of patients who needed further evaluation. NIPS serve a similar purpose.

Moreover, NIPS are not "problematic" just because they identify many more patients at increased risk of carrying a fetus with a rare disease than the number of fetuses actually expected to be born with such disease. This is completely expected when screening large populations for extremely rare diseases, even when the test has near perfect sensitivity and specificity. To demonstrate, if a screening test has 99.9% sensitivity and specificity, then 1 out of every 1,000 patients without the condition would still be expected to receive a positive screening result. But if fewer than 1 in 1,000 patients in the population are expected to have the condition based on disease prevalence, then the number of positive screening results in patients without the condition would necessarily exceed the number of positive screening results in patients who actually have the condition. For example, when applied to DiGeorge Syndrome, which affects 1 in 4,000 births, the NIPS test would be expected to identify five times as many potential cases than there would be confirmed diagnoses. As acknowledged by the *New York Times* article cited by FDA, in a population of 20,000 pregnant patients, a test with 99.9% sensitivity and specificity—nearly perfect analytical validity—would be expected to identify 25 patients at higher risk of carrying a fetus with DiGeorge Syndrome, even though only 5 of those patients would be expected to receive a confirmed diagnosis.[146] These results are not an indication that the test is unreliable.

As with all screening tests, the goal of NIPS is to identify patients at elevated risk of a disease or condition, in this case, pregnancies with elevated risk of having chromosomal or genetic abnormalities. The tests are not meant to be diagnostic, and patients should not be using screening tests to make decisions without obtaining appropriate diagnostic testing. To revisit an earlier analogy, a physician would not recommend a mastectomy on the basis of a mammogram alone without confirmatory testing. If patients and providers are making decisions on the basis of screening tests alone, then there is a need for better education on the role of these tests.

Second, FDA's mischaracterization of NIPS ignores the significant public health benefits of these screening tests. Without a screening test, the only information a pregnant patient can obtain about the genetic health of their fetus must be obtained by invasive diagnostic procedures like chorionic villus sampling (CVS) and amniocentesis. Both methods require collection of cells or fluids proximal to the fetus and carry a risk of miscarriage.[147] Moreover, CVS generally is not performed until 10-12 weeks of pregnancy (and may require follow-up blood tests between 16-18 weeks of

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[145] Indeed, this is the tradeoff for <u>all</u> screening tests. Screening tests will necessarily identify a greater number of patients with an elevated risk of having a particular condition than would be identified by a diagnostic test that identifies patients who definitively have a condition.

[146] 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.

[147] Mayo Clinic, *Amniocentesis*, MAYOCLINIC.ORG, https://www.mayoclinic.org/tests-procedures/amniocentesis/about/pac-20392914 (last visited Nov. 3, 2023); Johns Hopkins Medicine, *Chorionic Villus Sampling (CVS)*, HOPKINSMEDICINE.ORG, https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/chorionic-villus-sampling-cvs (last visited Nov. 3, 2023).

pregnancy), and amniocentesis generally is not performed until 14-20 weeks of pregnancy.[148] In contrast, NIPS utilizes a blood draw taken from the expectant patient, making it non-invasive, and can be performed around 10 weeks of pregnancy.[149] NIPS is also a significant improvement over the previously available screening technology—maternal serum screening (MSS)—which, while noninvasive, generally is not performed until 15-22 weeks of pregnancy and reportedly identifies more patients than NIPS for follow-up diagnostic testing that ultimately receive a negative diagnostic result.[150] The availability of NIPS to screen for common chromosomal abnormalities can help a large majority of patients avoid more invasive tests like CVS and amniocentesis that have greater associated risks, including infection and miscarriage. Indeed, multiple studies have confirmed a significant reduction in invasive prenatal procedures since the introduction of NIPS.[151]

Studies have confirmed the technical performance and clinical validity of NIPS using cell-free DNA,[152] and current clinical guidelines recommend NIPS for pregnant patients. For example, the current guidance from the American College of Obstetricians and Gynecology (ACOG) recommends that prenatal genetic screening, including NIPS, as well as diagnostic testing should be discussed with **"all pregnant patients regardless of maternal age or risk of chromosomal**

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[148] Mayo Clinic, *supra* note 147; Johns Hopkins Medicine, *supra* note 147.

[149] Society for Women's Health Research, *Understanding Genetic Screening and Maternal Care*, https://swhr.org/wp-content/uploads/2022/01/SWHR-Genetic-Screening-Poster-FINAL-2022Jan.pdf (last visited Nov. 3, 2023).

[150] John E Delzell, Jr., *What Can We Do To Prepare Patients for Test Results During Pregnancy?*, 173 WESTERN J. MED. 183 (2000), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1071060/; Mayo Clinic Laboratories, *Patient Education: Maternal Serum Screening*, MAYOCLINICLABS.COM, https://www.mayocliniclabs.com/-/media/it-mmfiles/Special%20Instructions/E/5/9/maternal%20serum%20screening%20patient%20information#:~:text=To%20receive%20maternal%20serum%20screening%20you%20must%20have,produced%20by%20the%20unborn%20baby%20and%2For%20the%20placenta (last visited Nov. 3, 2023); Illumina, *Comparing NIPT to other aneuploidy screening methods*, ILLUMINA.COM, https://www.illumina.com/clinical/reproductive-genetic-health/nipt/labs/nipt-vs-conventional-aneuploidy-screening.html (last visited Nov. 3, 2023).

[151] Sebastian Larion et al., *Association of Combined First-Trimester Screen and Noninvasive Prenatal Testing on Diagnostic Procedures*, 123 OBSTETRICS & GYNECOLOGY 1303 (2014), https://journals.lww.com/greenjournal/abstract/2014/06000/association_of_combined_first_trimester_screen_and.22.aspx; Kris Van Den Bogaert et al., *Outcome of Publicly Funded Nationwide First-Tier Noninvasive Prenatal Screening*, 23 Genetics in Med. 1137 (2021), https://www.gimjournal.org/article/S1098-3600(21)05214-X/fulltext; Lara A. Friel, Jennifer L. Czerwinski & Claire N. Singletary, *The Impact of Noninvasive Prenatal Testing on the Practice of Maternal-Fetal Medicine*, 31 AM. J. PERINATOLOGY 759 (2014), https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0033-1359717; Stephen J. Robson & Lisa Hui, *National Decline in Invasive Prenatal Diagnostic Procedures in Association with Uptake of Combined First Trimester and Cell-Free DNA Aneuploidy Screening*, 55 AUSTL. & N.Z. J. OBSTETRICS & GYNAECOLOGY 507 (2015), https://obgyn.onlinelibrary.wiley.com/doi/10.1111/ajo.12380.

[152] Nancy C. Rose et al., *Systematic Evidence-Based Review: The Application of Noninvasive Prenatal Screening Using Cell-Free DNA in General-Risk Pregnancies*, 24 GENETIC MED. 1379 (2022), https://www.gimjournal.org/article/S1098-3600(22)00714-6/fulltext.

abnormality," and among available screening options, "[c]ell-free DNA," i.e., NIPS, "is the most sensitive and specific screening test for the common fetal aneuploidies," though it is "**not equivalent to diagnostic testing**" (emphasis in original).[153] Notably, these guidelines supersede the 2012 ACOG statement that FDA cited in Reference 11 to the Proposed Rule, purportedly supporting that such tests should not, at that time, be used in the general, low-risk population.[154] Consistent with the available scientific evidence and clinical guidelines, payers have also recognized the value of NIPS and have made determinations that such tests yield useful and clinically valid information.[155]

3. FDA's characterization of oncology tests is inaccurate.

Finally, we are deeply disappointed in FDA's mischaracterization of LDTs developed and performed in the oncology field. Innovation in testing is of paramount importance to making advancements in the clinical care of oncology patients, but the Proposed Rule fails to recognize the important benefits of LDTs in this space. For example, long before there were any approved or cleared diagnostic test kits for evaluating genetic risk of developing certain hereditary cancers, high-complexity laboratories were developing and offering these tests, giving patients greater opportunity for clinical care. There are numerous examples of the lifesaving innovations pioneered by laboratories in this space. We noted several such examples in the prior sections: testing for BRCA mutations associated with breast and ovarian cancer, testing for KRAS mutations associated with non-small cell lung cancer, pancreatic ductal adenocarcinoma, and colorectal cancer, and NGS technology, more broadly. We also noted in prior sections how clinicians continue to rely on LDTs today to receive the most up-to-date information about their patients based on newly discovered and validated biomarkers.

Moreover, some of the references cited in the Proposed Rule regarding oncology LDTs are flawed and/or misconstrued. Two of the references warrant special attention: a study by Pfeifer et al. comparing reference samples (Reference 12 in the Proposed Rule) and the Friends of Cancer Research (FOCR) study on tumor mutational burden (TMB) LDTs (Reference 14 in the Proposed Rule).

First, the Proposed Rule cites a study by Pfeifer et al. that claims to have found that only 7 of 19 laboratories that tested the same samples with LDTs correctly reported all results.[156] This study

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[153] ACOG, *NIPT Summary of Recommendations*, POLICY PRIORITIES: CURRENT ACOG GUIDANCE, https://www.acog.org/advocacy/policy-priorities/non-invasive-prenatal-testing/current-acog-guidance (last visited Nov. 3, 2023).

[154] *See* FDA, THE PUBLIC HEALTH EVIDENCE FOR FDA OVERSIGHT OF LABORATORY DEVELOPED TESTS: 20 CASE STUDIES (2015) http://web.archive.org/web/20151122235012/https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf.

[155] Andrew P. Dervan et al., *supra* note 68 ("All payers studied cover cfDNA screening for detection of trisomies 21, 18 and 13 in high risk, singleton pregnancies, based on robust clinical validity (CV) studies and modeled evidence of clinical utility (CU). … Starting in August 2015, 8 of the 19 payers also began covering cfDNA in average risk pregnancies, citing recent CV studies and updated professional guidelines."), https://www.nature.com/articles/gim2016145.pdf.

[156] 88 Fed. Reg. at 68011.

has been discredited, however. In late September 2023, the CAP Molecular Oncology Committee reanalyzed the data from this study, adjusting for confounding conditions, and found that "laboratories consistently have high detection rates" for the tested variants.[157] Moreover, based on this reanalysis, the results from the original study cited by FDA "are not generalizable to all molecular oncology testing and should not be used to market products or change policy affecting all molecular oncology testing."[158]

Second, FDA cites the FOCR study to imply that TMB LDTs are unreliable, claiming the study "found substantial variability among [TMB] tests manufactured by laboratories."[159] However, the data from such study actually support that inter-assay variability of TMB LDTs is comparable to the variability observed between FDA-authorized assays. Specifically, in addition to LDTs, the study included two FDA-authorized IVD assays, and while the study did not conduct pairwise comparisons of TMB results between assays, a preliminary analysis based on data provided in the FOCR publication shows similar, and in some cases greater, variability between the FDA-authorized assays than between the FDA-authorized assays and LDTs included in the study.

Moreover, FDA's naked assertion that the FOCR study showed empirical variability among test results fails to recognize the important scientific and clinical context in which such test results are interpreted. As noted in the publication, the empirical variability across assays was observed to increase with increasing TMB value. But TMB test results are only semi-quantitative, and above a specified cutoff there is limited to no clinical impact for the patient. Even a high degree of variability at TMB values well above the cutoff would have limited to no clinical impact because variability would not cause results to fall below the cutoff. Importantly, these cutoffs are assay-specific to account for each assay's unique performance characteristics. However, differences in assay-specific cutoffs were not addressed or reported in this study.

Furthermore, the study was neither designed nor conducted to evaluate whether there was any clinical impact of observed variability among TMB tests from different laboratories. Rather, the study was designed and conducted as a collaborative effort including IVD and LDT assay developers to identify sources of variability between assays, to develop recommendations on the design of TMB assays, and to support transparency with the goal of furthering community understanding of TMB assays and results. Using the study to imply that LDTs may not provide accurate or reliable results misrepresents the design and results of this study.

Finally, other evidence cited by FDA is anecdotal and presented without important context. In particular, the Proposed Rule cites "[a]n article published earlier this year [that] detailed an oncologist's experience with false results from an unapproved blood-based multi-cancer detection IVD offered as an LDT and intended to screen for more than 50 types of cancer (Ref. 16)."[160] As an initial matter, as in the context of NIPS, cancer screening results are not "false" just because a definitive diagnostic test yields a different result. But beyond that point, this summation of the

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[157] Ahmet Zehir et al., *SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance*, ARCHIVES PATHOLOGY & LAB'Y MED. 1 (2023), https://meridian.allenpress.com/aplm/article/doi/10.5858/arpa.2023-0322-CP/496201/SPOT-Dx-Pilot-Reanalysis-and-College-of-American.

[158] *Id.*

[159] 88 Fed. Reg. at 68011.

[160] 88 Fed. Reg. at 68011.

reference leaves out important context about the analytical validity of the test at issue. The article tells the story of only one positive result in a patient determined not to have cancer, and one negative result in a patient who ultimately did have cancer. But as explained in the article, the oncologist in the story has encountered only one other "false positive" out of about 2000 test results in over 18 months, and "[s]he also discovered two positive signals for cancer … that were confirmed with follow-up tests," both of which were caught "remarkably early, in time for treatment."[161]

Finally, FDA itself has recognized the role that LDTs can play in informing treatment decisions in the oncology space. This past summer, FDA announced a pilot program that would allow certain oncology drugs that require companion diagnostics to be approved without a corresponding FDA-approved companion diagnostic.[162] Instead, FDA would publish information about the performance characteristics of the CTA used in clinical studies of the drug. With that information, laboratories would then be able to develop LDTs to inform patient treatment decisions.

For all of these reasons, FDA has mischaracterized LDTs in the preamble to the Proposed Rule. This faulty characterization cannot serve as the underlying rationale for imposing the ill-fitting device framework on LDTs. As discussed below, FDA's cost-benefit analysis for the Proposed Rule is also flawed and cannot support finalizing the Proposed Rule.

V. FDA's Cost-Benefit Analysis is Flawed in Numerous Ways and Cannot Support Finalizing the Proposed Rule.

FDA fails to grasp the impact that finalizing this proposed rule would have on laboratories, patients, and other stakeholders. ACLA strongly disagrees with the cost-benefit analysis in the Proposed Rule and the RIA. Below we summarize key points regarding how FDA (A) underestimates the costs of the Proposed Rule, and (B) overestimates the benefits of the Proposed Rule, that the Agency should consider and incorporate into any final regulatory impact assessment.

Additionally, as demonstrated by the analysis of Professor Chris Carrigan in Exhibit 1, FDA's economic assessment fails to adhere to the standards described in the academic literature as well as OMB's Circular A-4. These fundamental concerns result in an RIA that: 1) significantly understates costs by failing to quantify a key ancillary effect; 2) substantially inflates benefits by misusing benefit transfer methods; 3) provides limited ability to evaluate reasonable alternative regulatory approaches; and 4) offers minimal discussion of the distributional effects, including those on marginalized and underserved communities. ACLA incorporates by reference that analysis.

A. FDA underestimates the costs of the Proposed Rule.

Applying device regulation to LDTs, as proposed, would have significant negative impacts on the availability of tests that are available only as LDTs, innovation in diagnostic and laboratory science, and broader access to testing. However, FDA uses numerous assumptions and guesswork to derive its estimates of costs associated with the Proposed Rule. For an agency that seeks to ground its work in scientific analysis and robust evidence, this analysis is concerning.

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[161] Donavyn Coffey, *Blood Test Positive for Cancer, but Is There Really a Tumor?*, MEDSCAPE (Feb. 17, 2023), https://www.medscape.com/viewarticle/988431.

[162] *See* FDA, *Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program* (June 21, 2023), https://www.fda.gov/medical-devices/in-vitro-diagnostics/oncology-drug-products-used-certain-in-vitro-diagnostics-pilot-program.

As an initial matter, FDA made no attempt to collect information about the number of high-complexity CLIA laboratories or LDTs currently being offered that would be affected by the Proposed Rule, despite the Agency having the tools to do so. For example, FDA could have coordinated with other HHS agencies, CMS and CDC, to collect information from CLIA-certified laboratories regarding the number of laboratories that are high-complexity laboratories and the number of LDTs offered by each such laboratory. Laboratories applying for CLIA-certification must submit Form CMS-116, which requires a list of the non-waived tests the laboratory will offer, including whether the test is moderate- or high-complexity.[163] FDA also could have issued an RFI seeking information regarding the number of high-complexity clinical laboratories and the number of LDTs currently being offered.

FDA did not do any of this. Instead, FDA has proposed rulemaking on the basis of anecdotal evidence and extrapolations about the potential impact to industry, patients and other stakeholders. Under the Administrative Procedure Act, the Agency "must examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983). Where (1) key data is readily available to an agency, or (2) certain data is critical to the agency's decision but the agency fails to either make an effort to collect that data or explain why it was unable to collect it, a court should find that the agency failed to "examine the relevant data and articulate a satisfactory explanation for its action." *See, e.g., Rural & Migrant Ministry v. EPA*, 565 F. Supp. 3d 578, 599–600 (S.D.N.Y. 2020); *Innovator Enterprises, Inc. v. Jones*, 28 F. Supp. 3d 14, 26 (D.D.C. 2014). This is not a scenario where the data is unobtainable, nor is there a valid reason for FDA not having the data. *See F.C.C. v. Fox Television Stations, Inc.*, 556 U.S. 502, 519 (2009) (explaining that there "are some propositions for which scant empirical evidence can be marshaled" and that "it is one thing to set aside agency action under the Administrative Procedure Act because of failure to adduce empirical data that can readily be obtained [and] something else to insist upon obtaining the unobtainable.").

As a result of FDA proceeding without data necessary to support its analysis, FDA has significantly underestimated the costs of complying with the Proposed Rule. As explained further below, this underestimate stems from a number of errors in FDA's analysis, including:

- Underestimating the number of affected laboratories, the number of LDTs that are currently available, and the number of LDTs that laboratories develop annually;
- Underestimating the number of currently available LDTs and new LDTs that would require different premarket submissions;
- Underestimating the cost of test validation and preparation of premarket submissions for LDTs; and
- Underestimating the cost of compliance with other device regulations for LDTs.

When these costs are more accurately estimated, the negative consequences for laboratories, patients, FDA, and other stakeholders are immense. As explained earlier in these comments, these

[163] Form CMS-116, *Clinical Laboratory Improvement Amendments (CLIA) Application for Certification* (12/21), https://www.cms.gov/medicare/cms-forms/cms-forms/downloads/cms116.pdf.

costs include removal of important tests from test menus due to the cost of compliance, and not due to any reliability or accuracy concerns; significant slow-down in diagnostic innovation by laboratories due to competing demands for limited resources; reduced testing capacity at laboratories due to competing demands for limited resources and potential closures of laboratories; and slower availability for innovative diagnostics due to constrained resources at FDA.

1. *FDA has underestimated the number of affected laboratories, the number of LDTs that are currently available, and the number of LDTs that laboratories develop annually.*

FDA has estimated there to be approximately 1,200[164] laboratories that would be affected by the Proposed Rule and that such laboratories offer, on average, 67 tests per laboratory, leading to an estimate of 80,400 tests potentially affected. FDA reached those estimates by extrapolations from the New York State database of tests, but publicly available sources support estimates that are higher. For example, in CMS's most recent update to the CLIAC, the agency reported 34,266 laboratories that have a certificate of compliance or accreditation, i.e., 34,266 laboratories that perform moderate- and/or high-complexity testing.[165] It is unlikely that only 3.5% of these laboratories perform high-complexity testing and offer LDTs, as suggested by FDA's estimates.

FDA's estimate of 67 tests per laboratory also is far too low. Several ACLA members report offering hundreds or even thousands of LDTs. And this number would align with other publicly available estimates of LDTs. For example, a paper by Halbisen and Lu in 2023[166] found that as of November 2022, there were a total of 37,106 genetic tests offered in the US for clinical purposes. The paper also estimates that in 2022, 3,097 new genetic tests were made available. Assuming that an equivalent number of new tests were first offered in 2023 (99.5% of which are clinical tests), the total estimate for genetic tests alone on the US market is 40,000 tests. This estimate is limited to genetic tests, almost all of which are offered as LDTs. FDA's estimate also does not account for LDTs that would continue to be introduced from now until whatever time that premarket submissions are required under any final phaseout policy, likely adding tens of thousands of additional tests.

Similarly, FDA has significantly underestimated the number of new LDTs that would become subject to regulation. FDA has estimated that 7,776 new LDTs would be offered each year, based on an estimated average of 6 new LDTs per laboratory per year, adjusted to account for LDTs offered by new laboratories. But as noted above, the Halbisen and Lu paper estimates that, for genetic tests alone, 3,097 new tests were made available in 2022.[167] Moreover, as the RIA acknowledges, some large reference laboratories may develop as many as 100 new LDTs per year. Further, adjustments and updates to FDA-regulated tests would trigger the need for new FDA submissions. FDA needs to account for this reality.

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[164] For purpose of these comments, we rely on FDA's "primary" estimates throughout the RIA. But of course the RIA accounts for a range of costs.

[165] Gregg Brandush, *CMS CLIA Update, Division of Clinical Laboratory Improvement and Quality* (Nov. 9, 2023), https://www.cdc.gov/cliac/docs/november-2023/2_CMS_Update.pdf.

[166] *See* Alyssa L. Halbisen & Christine Y. Lu, *supra* note 122.

[167] *Id.*

2. FDA's estimates regarding premarket review are misguided.

With respect to LDTs that are currently offered, the Proposed Rule assumes that 4,210 tests would require a PMA Submission, 4,020 would require a De Novo, 32,160 would require a 510(k), and the rest would be exempt from premarket review. This is a significant underestimate across submission types. FDA's underestimate stems from several mistakes including: (1) underestimating the total number of LDTs that would require a premarket submission; (2) underestimating the ratio of LDTs that are novel and would require PMA approval or De Novo Classification; and (3) overestimating the ratio of LDTs that would be 510(k)-exempt.

First, as explained above, FDA has underestimated the number of currently available LDTs. Accordingly, even if FDA were correct that of all existing LDTs, only 5.2% would require PMA Submissions, only 5% would require De Novo requests, and only 40% would require 510(k)s, FDA would receive far more submissions—PMA Submissions, De Novos, and 510(k)s—than it anticipates.

Second, FDA has underestimated the number of LDTs that are novel and would require PMA approval or De Novo Classification. As discussed earlier in these comments, novel LDTs that lack a predicate device would require PMA approval or a De Novo classification because their technologies have surpassed that of FDA-cleared/approved devices, or because they are intended for a use for which there is no cleared/approved alternative. For example, as stated above, there are currently approximately 40,000 genetic LDTs currently available, and there are not currently available class I or class II genetic tests that could serve as predicate devices. The vast majority of these genetic LDTs would be required to undergo the PMA or De Novo process. Other testing methodologies rely entirely on LDTs. For example, as described above, virtually all mass spectrometry testing is done by LDTs.

The conclusion that most LDTs would require a PMA or De Novo is supported by FDA's own data. In the MDUFA V Fourth Quarter Performance report, the Agency reported that of 7 LDT submissions it received in FY2023, 5 were for PMAs, 1 was for a De Novo, and only 1 was for a 510(k).[168] Throughout the entirety of MDUFA IV, the Agency reported that of the 49 LDT submissions it received in FY2018 through FY2022, 28—over half—were PMAs, 10 were De Novos, and 11 were 510(k)s.[169]

Third, FDA also has overestimated the ratio of LDTs that would be 510(k)-exempt and, accordingly, significantly underestimated the number of LDTs that would require a premarket submission. FDA has estimated that 50% of LDTs would be 510(k)-exempt, but this is wrong. Only a small number of LDTs would fall within a 510(k) exemption. Rather, in most cases, a 510(k) submission or a PMA supplement would be required because the laboratory is offering a modified version of a cleared or approved IVD. For all of these reasons, FDA's estimates of 4,210 PMA Submissions, 4,020 De Novo applications, and 32,160 510(k) submissions for existing LDTs is dramatically understated.

FDA's estimates regarding new and modified LDTs that would be subject to premarket review on an ongoing basis suffer from similar flaws. ACLA disagrees with FDA's estimate that, each year,

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[168] FDA, *Quarterly Update on Medical Device Performance Goals --- MDUFA V CDRH Performance Data --- Actions through 30 September 2023* (Nov. 16, 2023), https://www.fda.gov/media/173923/download?attachment.

[169] FDA, *MDUFA IV (FY 2018-2022) Performance Report* (Nov. 16, 2023), https://www.fda.gov/media/173924/download?attachment.

FDA would receive 407 PMA Submissions, 389 De Novo requests, and 3,110 510(k) submissions. This is based on an estimated 7,776 new LDTs per year, and as noted above, this is a significant underestimate. Even if FDA's estimated percentages were correct (5.2% PMA Submissions, 5% De Novos, and 40% 510(k)s), far more tests would require premarket submissions than estimated. But FDA is wrong about those estimates for the same reasons described above for existing tests. Accordingly, FDA would receive significantly more PMA Submissions and De Novos for novel tests that lack a predicate device, as well as 510(k)s for non-exempt tests.

3. FDA has underestimated the cost of test validation and preparation of premarket submissions for LDTs.

Moreover, FDA has grossly underestimated the costs of bringing an LDT through the premarket review process. FDA estimates that costs of preparing and submitting a premarket submission is approximately $4.38 million for a PMA, $564,674 for a De Novo Classification Request, and $274,930 for a 510(k) requiring a method comparison study or $526,182 for a 510(k) requiring a moderately complex clinical study. However, these estimates do not reflect the real-world costs of conducting additional studies to support premarket submissions, and other elements of the cost estimates are unrealistically low. Earlier in these comments, we discussed the significant challenges of conducting validation studies according to FDA's requirements to support clearance or approval of tests. But even if those challenges could be overcome, the costs of test validation and premarket submissions is significantly higher than FDA estimated in its RIA.

With respect to costs not reflected in FDA's estimates, preparation of submissions for existing tests would require laboratories to re-validate their existing tests because FDA's design controls under 21 CFR section 820.30 cannot be applied retroactively to an already-designed test. However, FDA's RIA falsely claims that in estimating the costs of PMA, 510(k) and De Novo requirements, it can "exclude[] costs that would already be part of compliance with the QS requirements under Stage 3, including costs of developing design controls,"[170] even though FDA's one-time cost assessment for compliance with QS requirements under Stage 3 does not account for these requirements. Specifically, although the one-time cost assessment for Stage 3 includes general design controls under 21 CFR section 820.30(a), it does not include design and development planning, design review, design verification, design transfer, design changes, or the design history file under 21 CFR section 820.30(b) through (j). All of these elements are required for a compliant quality system to support a PMA approval, De Novo classification, or 510(k) clearance. They are conspicuously missing from FDA's RIA, and they must be considered either under Stage 3 as part of the one-time annual cost of compliance with QS requirements or under Stages 4 and 5 as part of the cost for bringing a premarket submission to FDA.

Moreover, even if FDA exercised some flexibility with regard to leveraging existing validation studies, FDA's estimates do not consider the costs associated with conducting additional validation studies to satisfy FDA's expectations where those studies were not required under existing regulatory frameworks. As discussed earlier in these comments, FDA often requires additional validation data that laboratories and other reviewing entities (e.g., CLIA, CAP, New York State) have not determined to be necessary.

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[170] FDA, PRELIMINARY REGULATORY IMPACT ANALYSIS; INITIAL REGULATORY FLEXIBILITY ANALYSIS; UNFUNDED MANDATES REFORM ACT ANALYSIS 76-77 (2023), https://www.fda.gov/media/172557/download?attachment ("RIA").

Other costs also are significantly underestimated. As just one example of many, FDA estimates that identifying a predicate device for a 510(k) would require only 1.5 hours, costing only $123.48. While that theoretically could have been true in the past and in the simplest of cases for an experienced regulatory professional, it would take laboratories inexperienced with FDA's regulatory regime much, *much* longer to identify an appropriate predicate today, especially in the context of FDA's evolving policies related to the 510(k) program. In particular, even if *a* predicate could be identified in a short amount of time, it would take much, much longer to identify a predicate device according to FDA's "best practices" as announced in draft guidance in September.[171] According to this draft guidance, it is not enough to identify a "valid" predicate; sponsors are expected to identify a valid predicate that: (1) has been cleared using "well-established methods," (2) continues to meet or exceed safety performance expectations, taking into account post-market reports of design-related malfunctions and adverse events, (3) does not have "unmitigated use-related or design-related safety issues," including consideration of FDA safety communications; and (4) is not subject to "an associated design-recall." Understanding these requirements, let alone applying them, would take significantly longer than 1.5 hours, even for a seasoned FDA regulatory professional.

FDA also underestimates the costs of conducting required clinical studies. The RIA estimates that clinical studies would cost approximately $2.83 million for a PMA, $311,553 for a De Novo Classification Request, and $314,065 for a 510(k). However, these clinical studies can be far more expensive. One ACLA member was required to pay $2,000 per sample for a colorectal test. Based on that cost, a single submission requiring 650 supporting samples at a cost of $2,000 for each sample would cost $1,300,000 just to obtain relevant samples.[172] And that cost does not include the numerous other costs associated with running clinical studies, preparing applications, interacting with FDA, and otherwise processing applications. FDA also fails to recognize that access to appropriate tissue samples and orthogonal test methods are severely limited for certain types of tests.

Other examples of underestimates of costs include FDA's estimates for preparing regulatory submissions and holding pre-submission meetings. FDA estimates that the total cost of preparing a regulatory submission for a De Novo Classification Request is only $124,998, failing to recognize the greater cost of the FY2024 user fee for such submission ($145,068). FDA also estimates the costs of pre-submission meetings with FDA are only $2,000 to $2,500 across submission types, but sponsors spend significant amounts of time preparing pre-submission requests, reviewing initial feedback from FDA, and preparing for and holding meetings with the Agency. Moreover, a novel assay may require *several* pre-submission meetings. FDA's suggestion that sponsors spend only $2,000 to $2,500 of time and resources to prepare for such meetings is a gross underestimate.

4. FDA has underestimated the cost of ongoing compliance with other aspects of device regulations.

Finally, FDA underestimates the costs of ongoing compliance with other aspects of device regulations, even when premarket submissions are not required. For Stage 1, FDA bases its cost estimate for complying with medical device reporting (MDR) requirements on the approach taken

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[171] FDA, DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF: BEST PRACTICES FOR SELECTING A PREDICATE DEVICE TO SUPPORT A PREMARKET NOTIFICATION [510(K)] SUBMISSION (2023), https://www.fda.gov/media/171838/download.

[172] An estimate of 650 samples is based on FDA-approved assays in various clinical areas. For example, Roche's Elecys Phospho-Tau CSF assay was required to be clinically validated with 646 samples. Sample types such as cerebral spinal fluid would likely be far in excess of $2000/sample.

for its 2014 final rule on *Medical Device Reporting: Electronic Submission Requirements*, which is an inappropriate comparison. This rule revised existing postmarket medical device reporting requirements as applicable to manufacturers already familiar with MDR reporting requirements. Laboratories, however, would start from scratch. It would not be sufficient to modify existing SOPs. Wholly new SOPs for complaint evaluation and MDRs would be required and employees would need to be educated and trained on these procedures. FDA's cost estimate for complying with corrections and removals reporting requirements, based on its 2020 notice, *Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals*, suffers from the same flaw.

For Stage 2, FDA's cost estimates for complying with registration and listing, labeling, and investigational use requirements suffer from the same flaws as in Stage 1, plus additional complexities specific to the nature of LDTs. For example, FDA estimates that a general/operations manager would require 3 hours to complete registration and listing for a single establishment and the LDTs offered therein. However, before laboratories can list their LDTs, they first must complete a regulatory assessment of the likely classification of each LDT, i.e., determine whether any particular LDT is class I, class II, or class III, and determine within which classification regulation/product code the LDT fits. For laboratories inexperienced in FDA regulation and classification of medical devices, this would be a significant undertaking and require *far* more than 3 hours to complete for FDA's estimated 67 LDTs per laboratory. And such regulatory analysis would be extremely consequential, likely driving the laboratory's strategy for premarket submissions, to the extent submissions would be pursued. Accordingly, laboratories could not rush through such analysis to satisfy FDA's registration and listing requirements. Furthermore, FDA's tables outlining costs of registration and listing also do not appear to include the annual registration fee, which in FY2024 would be $7,653 *per laboratory*. There currently are no waivers or reductions for registration and listing fees for small establishments, businesses, or groups.

With respect to labeling, FDA estimates that a general/operations manager would require 20 hours to redesign existing labeling for LDTs to comply with labeling requirements. However, it is not clear—at all—what the labeling requirements are for LDTs. Because LDTs are not a product, they have no packaging to which a label could be applied, nor are there existing instructions for use beyond the laboratory's procedure manual. FDA has not addressed how laboratories are expected to comply with labeling requirements, and even if FDA forces out a draft guidance within a year after finalization of the Proposed Rule, laboratories would be left scrambling to figure out how to comply by Stage 2 of the phaseout policy. Furthermore, 20 hours is a gross underestimate of the time required to additionally design and implement new processes to meet the labeling controls requirements in 21 CFR Part 820.

FDA also dramatically underestimates the costs of complying with investigational use requirements. As an initial matter, FDA's estimate that only 6.75% of investigational LDTs would require an application for an investigational device exemption (IDE) is flawed. This assumption is based on (1) the number of IDE applications FDA currently receives divided by the number of IVD marketing submissions FDA ultimately receives, and (2) FDA's assumption that only 50% of LDTs would require a premarket submission. As discussed earlier, FDA's assumption that only 50% of LDTs would require a premarket submission is deeply flawed. Moreover, this estimate completely ignores clinical trial assays developed solely for the purpose of supporting drug/biological clinical trials, where those assays are never intended for commercialization as a diagnostic assay. For example, screening patients for trials often requires development of *several* CTAs by different laboratories across the country to identify sufficient eligible patients for enrollment. Where the assays affect treatment of patients in a clinical trial, an IDE application may be necessary for *each*

CTA, even though only *one* marketing submission for a companion diagnostic may ultimately be submitted. FDA has failed to consider these CTAs in its estimate.

Additionally, FDA's estimates of the costs of complying with investigational use requirements ignores the costs of complying with the abbreviated requirements for non-significant risk devices. FDA's estimate of costs applies only to those investigational LDTs that would require an IDE application. However, non-exempt investigational LDTs that are not significant risk also must comply with abbreviated requirements related to labeling, IRB approval, informed consent, monitoring, recordkeeping, and reporting.[173] FDA has failed to consider the costs of compliance for non-significant risk LDTs used in clinical trials.

FDA also has underestimated the costs of ongoing compliance associated with quality system requirements. Aligning current laboratory quality requirements under CLIA, CAP, international standards such as the International Organization for Standardization (ISO) 15189, New York State Department of Health, and other applicable state laws with a shifting FDA quality regime is a complex exercise. FDA estimates that establishing an FDA-compliant quality system would require only $60,466 per laboratory for one-time costs,[174] but this estimate fails to account for some of the most significant quality requirements related to design controls, purchasing controls and acceptance activities. Table 23 of the RIA lists the one-time annual requirements for establishing an FDA-compliant quality system, but it accounts only for "general" design controls under 21 CFR section 820.30(a) and does not account for any other design control requirements under 21 CFR sections 820.30(b) through (j), as discussed above, nor does it account for purchasing controls under 21 CFR section 820.50 or acceptance activities under 21 CFR sections 820.80 and 820.86.[175] All of these quality system requirements are fundamental to demonstrating that a device is manufactured consistent with FDA's quality requirements.[176] Accordingly, FDA's estimates for establishing a compliant quality system are deceivingly low.

Furthermore, FDA does not even attempt to quantify the costs of laboratories grappling with the shifting quality system requirements as FDA considers finalizing amendments to the quality system regulation to incorporate by reference the 2016 edition of ISO 13485, Medical devices – Quality management systems for regulatory purposes. Even if the requirements of this ISO are similar in some respects to the current quality system regulation under 21 CFR Part 820, shifting to

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[173] *See* 21 CFR § 812.2(b)(1).

[174] Estimated based on dividing FDA's estimate for one-time costs ($72.56 million) over FDA's estimate of affected entities (1,200).

[175] RIA Table 29.

[176] One potential rationale for excluding these elements may be that they are particularly relevant to supporting a marketing submission (PMA, De Novo, or 510(k)) for a device, such that they should be considered part of the cost of pursuing marketing authorization for tests, but FDA expressly excludes the design control requirements from their cost estimates for compliance with Stages 4 and 5 of the phaseout policy. *See* RIA at 76-77 ("We have excluded costs that would already be part of compliance with the QS requirements under Stage 3, including costs of developing design controls, acquiring GMP-compliant manufacture capability, and developing a risk management system."). Moreover, including such costs only under Stages 4 and 5 would fail to recognize that compliance with these elements of the quality system also apply to 510(k)-exempt LDTs, which, by FDA's estimate, would account for 50% of LDTs. It would also fail to account for the cost of establishing and implementing an entire design control process, independent of any particular LDT.

this new standard in the midst of a regulatory overhaul for LDTs would necessarily increase the costs to laboratories attempting to establish an FDA-compliant quality system. For example, responsible laboratories acting expeditiously to establish a quality system under 21 CFR Part 820 would incur additional costs when the regulation changes to reference ISO 13485, and they are forced to revisit completed work to incorporate this changed standard. FDA has not considered the impact of this shifting regulation on the costs of compliance for laboratories.

B. The claimed benefits of the Proposed Rule are dramatically overstated.

FDA claims that the Proposed Rule would generate substantial benefits and cost savings. The Agency claims that FDA regulation of LDTs would alleviate misdiagnoses and incorrect treatments that result from LDTs, promote more timely diagnoses, and reduce legal costs associated with lawsuits. FDA's benefit calculations are entirely speculative, relying on a number of shaky assumptions and questionable analytic steps. Moreover, the underlying studies cited by the Agency to support its analysis are flawed and cannot be used to generalize across LDTs.

1. FDA's overall approach to calculating the benefits of the Proposed Rule is fundamentally flawed.

Before turning to the specific evidence cited by FDA in its benefit calculations, there are several overarching flaws in FDA's approach. As we discussed previously, the LDTs cited by FDA in its benefits calculation represent a vanishingly small fraction of the number of LDTs available today and relied upon by physicians. FDA could have begun this regulatory process by requesting data from the laboratory community on the performance of LDTs, so that a systematic or more representative analysis could have been included in the Proposed Rule and RIA. FDA chose not to do that. Instead, FDA opted to go forward with a Proposed Rule and RIA by selecting a handful of examples and then extrapolating those isolated examples to the entire laboratory community. Extrapolating claimed misdiagnoses – using cherrypicked examples, while simultaneously ignoring other evidence of high quality LDTs – is inappropriate. This raises the same concerns expressed above regarding FDA's failure to "examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983).

Further, although FDA pays lip service to the fact that no test is perfect, the analysis employed starts with the premise that if LDTs were regulated as devices, problems associated with inaccurate test results would all but evaporate. That is obviously not the case. No diagnostic test, whether offered as an LDT or offered as an FDA-approved or -cleared test, is 100% accurate. Stated differently, every test has a certain sensitivity and specificity, reflecting that false positives and false negatives are expected in some number of patients. These risks are unavoidable and well accepted. Depending on a variety of factors, the sensitivity and specificity may be relatively high (e.g., in some cases exceeding 99%), but in other cases, the sensitivity and specificity may be lower. FDA knows this. For example, in 2022, FDA cleared a De Novo application for an assay to detect kidney stress in patients at risk of acute kidney injury. In clinical validation studies, the data reflected the test's sensitivity ranged from 76% to 93% and the test's specificity ranged from 45% to 51%.[177] Notwithstanding that level of accuracy, FDA rightly concluded that the value of having this tool available to clinicians outweighed the potential for false negative and false positive results.

[177] *See* FDA, De Novo Decision Summary: DEN130031, https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130031.pdf (last visited Nov. 14, 2023).

Moreover, even when the sensitivity and specificity are quite high (e.g., 99%), such tests will necessarily yield a number of false results when the prevalence of a condition is extremely rare. Furthermore, there have been many recalls of FDA-approved or -cleared diagnostics for quality or other issues that impact the accuracy of those tests.[178]

Were FDA to conduct an impact analysis that uses only IVD kits with relatively high false positive/negative rates, IVDs for use in rare disease populations, and recalled devices, and then extrapolate those results to the entire IVD industry, the results would be poor. Such an analysis would likely conclude that FDA-approved or -cleared assays are causing innumerable harms to the health care industry and that a different FDA regulatory regime, assumed to cure all the claimed problems, would yield significant benefits. That would be a wholly inappropriate and unfair analysis. But that is exactly what FDA has done here. It has identified a small handful of LDTs, portrayed those examples in the worst light possible, extrapolated those results to the entire LDT community, and then made an assumption that FDA regulation would cure all faults. This is not a fair picture of LDTs and not an accurate picture of the benefits that could result from FDA regulation of LDTs as devices.

Finally, FDA's benefit calculations flow from claimed inaccuracies associated with LDTs and an assumption that each inaccurate result associated with an LDT leads to a misdiagnosis and/or inappropriate treatment decisions. But in virtually every case, diagnostic testing is used in connection with other assessment tools and clinical judgment. Again, FDA knows this. For example, the cleared intended use of the kidney stress test system cited above states that the test "is intended to be used in conjunction with clinical evaluation in patients who currently have or have had within the past 24 hours acute cardiovascular and or respiratory compromise and are ICU patients as an aid in the risk assessment for moderate or severe acute kidney injury (AKI) within 12 hours of patient assessment." In other words, clinicians should interpret the output of the diagnostic test in conjunction with other assessment and clinical judgment. LDTs are no different. Physicians and other clinicians must take the output of the test and consider it together with other resources and experience. The result of the assay is one input – usually amongst many inputs – used to decide on a course of treatment for a patient. FDA's analysis must account for this.

2. *FDA's estimates rely on flawed studies and examples.*

    a) The data and studies underlying FDA's estimate of expected reduction in misdiagnosis are flawed.

FDA estimates the probability of misdiagnosis from "problematic LDTs" by considering three probabilities: (1) the probability that a misdiagnosis occurs after testing with an IVD (as opposed to another method of diagnosis); (2) the probability that that an LDT was used in the diagnosis; and

[178] *See, e.g.*, FDA, *Remel, Inc. Recalls Thermo Scientific Gram Negative IVD AST Sensititre Plate for Risk of Potential False Susceptible Results*, https://www.fda.gov/medical-devices/medical-device-recalls/remel-inc-recalls-thermo-scientific-gram-negative-ivd-ast-sensititre-plate-risk-potential-false (last visited Nov. 11, 2023); FDA, *Class 2 Device Recall therascreen KRAS RGQ PCR Kit (24)*, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRes/res.cfm?id=203179 (last visited Nov. 11, 2023).

(3) the probability that the LDT was "problematic."[179] To the extent that these probabilities are supported by underlying studies (and one is not), those studies are flawed.

First, FDA assumes that "50% of misdiagnoses occur after testing" with an *in vitro* diagnostic test, presumably including both IVDs and LDTs. There is no data underlying this estimate. Moreover, as explained above, the result of the assay is one input – usually amongst many inputs – used to decide on a course of treatment for a patient. Even if a misdiagnosis occurs after use of a diagnostic test, it is wrong to attribute that misdiagnosis to the test alone.

Second, FDA significantly overestimates the probability that an LDT is used to diagnose a patient, and accordingly, overestimates how many misdiagnoses may be avoided if so-called "problematic" LDTs were removed from the market. In its RIA, FDA quotes a 2023 report from Grand View Research that "LDTs constitute about 50% of total *in vitro*-diagnostics devices that are used in some laboratories."[180] FDA then extrapolates this single statistic to estimate that "50% of IVDs are IVDs offered as LDTs." It is wrong to extrapolate this single statistic that applies only to "some laboratories," and it is also a gross overestimate based on other available data. Although there is a very high number of LDTs currently available and more are being developed every day, the ratio of LDTs versus IVDs performed in the clinical setting is significantly less than 50%. In a study by Rychert, et al., laboratory test orders at an academic medical center were reviewed to determine how frequently LDTs were ordered by clinicians.[181] The study found that of over 3 million tests ordered in a single year, only 116,583 (3.9%) were LDTs. The volume was higher in the cancer center compared with the university hospital (5.6% versus 3.6%, respectively), but nowhere near FDA's estimate of 50% of all tests ordered. The study also found this in the context of LDTs constituting a higher proportion of the distinct assays that were ordered. Of 1,954 distinct assays ordered over the course of the study, 880 (45%) were LDTs. This study supports that while there is a very high number of distinct LDTs that have been developed and innovated by laboratories, the rate at which they are used compared to IVDs is much lower than FDA estimates. Accordingly, FDA's estimates that 50% of diagnostic errors would be avoided by FDA regulation of LDTs is inaccurate and must be reassessed by the Agency.

Third, FDA has significantly overestimated the number of LDTs that are "problematic." FDA relies on the SPOT/Dx Pilot Publication authored by Pfeifer et. al from 2022, which FDA cites in support of the notion that 47% of LDTs are "problematic."[182] The SPOT/Dx pilot found that 9 out of 19 oncology LDTs had significantly lower performance than FDA-approved companion diagnostics. FDA then extrapolates that result to assert that there are potentially a significant number of deaths associated with preventable misdiagnoses due to problematic LDTs. Extrapolating yet further, FDA asserts that device regulation of such tests would prevent these misdiagnoses and would therefore result in savings of $27.7B (VSLY 3%). As an initial matter, it is inappropriate to use this single,

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[179] RIA at 37. FDA considers a fourth probability, the probability of misdiagnosis being associated with a fatality, to calculate the annual fatalities due to misdiagnosis.

[180] RIA at 38 (citing GRAND VIEW RESEARCH, LABORATORY DEVELOPED TESTS MARKET SIZE, SHARE & TRENDS ANALYSIS REPORT BY TECHNOLOGY (IMMUNOASSAY, MOLECULAR DIAGNOSTICS), BY APPLICATION (ONCOLOGY, NUTRITIONAL & METABOLIC DISEASE), BY REGION, AND SEGMENT FORECASTS, 2023 – 2030 (2023)).

[181] Jenna Rychert et al., supra note 18.

[182] John D Pfeifer et al., *Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics,* 157 AM. J. CLINICAL PATHOLOGY 628 (2022).

small study to characterize the performance of all LDTs across multiple disciplines. But even if it were sound scientific practice to extrapolate from a single study (which it is not), relying on the Pfeifer study is not appropriate. A more recent analysis of the SPOT/Dx pilot data by Zehir et al., using proficiency testing methods, reached a fundamentally different conclusion.[183] Specifically, by adjusting for confounding variables, the reanalysis found that LDTs had comparable performance to FDA-regulated tests. Moreover, Zehir et al. also conducted an assessment of LDTs based on data from CAP proficiency testing programs and found that the overall detection rates for single nucleotide variants (SNVs) and multinucleotide variants (MNVs) were 97.2% (2,671 of 2,748) and 91.8% (1,853 of 2,019), respectively. The paper concludes that "CAP PT program data demonstrate that laboratories consistently have high detection rates for KRAS and NRAS variants." In addition, the authors warn that the "SPOT/Dx pilot results are not generalizable to all molecular oncology testing and should not be used to market products or change policy affecting all molecular oncology testing."

b) The examples on which FDA relies to extract claimed benefits from regulating LDTs are flawed.

In addition, FDA's RIA attempts to extract supposed benefits of regulating LDTs from isolated problems with COVID tests. As we have previously noted, FDA's Proposed Rule dramatically distorts the COVID experience and the role that laboratories played throughout the pandemic. FDA's RIA again cites its flawed analysis of the first 125 COVID EUA requests submitted to FDA. As we have discussed above, it is wholly misleading for FDA to use the first EUA requests – submitted in rush of activity in order to contribute to the public health, often before relevant guidance from FDA was available – as a basis for evaluating COVID tests more broadly, much less for evaluating LDTs more broadly. But in its RIA, FDA takes it a step farther. FDA refers to a single LDT for COVID offered in Chicago. But as FDA well knows, it is impossible to extrapolate that single test to a broader basis to evaluate LDTs. Moreover, the laboratory at the center of this story engaged in fraud and was out of compliance with CLIA. Even if the laboratory leveraged only cleared and approved IVDs, the results would likely have been the same. FDA regulation would not have changed the outcome.

The other examples that FDA relies on for claimed benefits suffer from similar flaws. For example, FDA points to a single laboratory test called StatinCheck that, in FDA's view, lacked clinical validity, and NIPS tests. FDA fails to explain why the StatinCheck test lacks clinical validity, making an evaluation of FDA's claimed benefits impossible. Similarly, FDA cites NIPS tests and potential issues with false positive results associated with rare variants. As we previously noted, FDA has the NIPS story exactly backward. Laboratories that pioneered NIPS testing should be lauded for their remarkable contribution to the public health and reducing health care costs. Prior to NIPS, women would either skip the screening step and proceed directly to invasive diagnostic tests that are associated with higher incidence of adverse events and higher costs or they would proceed first with a different screening method that identified far more women for follow-up, invasive diagnostic testing than identified through NIPS. NIPS is highly accurate and has reduced the rate at which women routinely seek invasive diagnostic testing, thus reducing the number of women unnecessarily exposed to such risks.[184] Although it is true that certain very rare variants are associated with false

[183] Ahmet Zehir et al., *supra* note 157.

[184] *See, e.g.*, Rifat Mokhtar et al., *Comparing Non-invasive Prenatal Testing With Invasive Testing for the Detection of Trisomy 21*, 14 CUREUS e31252 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9733793/ ("The high performance and effectiveness of NIPT are undeniable.").

positive results, that is a necessary function of ensuring that such tests have sufficient sensitivity to detect true positive rare variants. This is why NIPS are not intended as definitive diagnostic tests for such rare diseases and should not be used in that way. But the fundamental point is that NIPS tests have advanced the public health immeasurably. It is improper for FDA to ignore the obvious benefits of LDTs that are offered as NIPS.

3. FDA's analysis excludes studies showing the value of LDTs.

FDA ignores other studies demonstrating that LDTs perform at least as well as FDA-approved or -cleared IVDs. For example, a 2017 study by Kim et al.,[185] compared the performance of LDTs and FDA-approved assays for key biomarkers used for companion diagnostics, including BRAF, EGFR, and KRAS mutations. That analysis found that in "6,897 proficiency testing responses, both LDTs and FDA-CDx exceed 97% accuracy combined across all comparable molecular oncology proficiency testing samples." The study concluded that "[t]hese findings support both the excellent and equivalent performance of both LDTs and FDA-CDx in clinical diagnostic testing." Further, the study observed that many laboratories using FDA approved CDx modified those tests to "allow for more clinical practice variety."

Other recent studies have affirmed the value of LDTs in improving care and saving lives. As one example, in 2021, Dimmock et al. published the results of "Project Baby Bear," which evaluated the benefits of implementing whole genome screening protocols in five California hospitals.[186] Specifically, acutely ill patients who were less than one year old and within one week of hospitalization or had just developed an abnormal response to therapy, were screened by an LDT using rWGS-based rapid precision medicine (RPM). The study evaluated two prespecified primary outcomes—changes in medical care because of rWGS results and changes in the cost of care because of rWGS at 4 months, 12 months, and 18 years after return of results. The results were clear – rWGS proved to be a valuable tool in clinical decision making. Of the 184 babies whose DNA was sequenced in this project, rare genetic diseases that explained the infant's admission were diagnosed in 74 babies (40%), genetic variants of uncertain significance (VUSs) were identified in 21 babies (11%), and no diagnosis was made in 89 babies (48%). Most diagnoses were of very rare disorders that would not be expected to have been seen by the child's providers previously in their careers. The authors of the paper concluded that "the five-site quality improvement project known as Project Baby Bear developed a real-world system for the rapid delivery of whole-genome sequencing that improved outcomes and decreased costs of care. This project has demonstrated that hospitals and payors with similar systems of rapid precision medicine can deploy rWGS for critically ill children in a cost-effective manner."

As the above discussion and examples illustrate, the Proposed Rule and RIA cherry-pick allegedly poor performing tests in an effort to extrapolate significant economic benefits from FDA regulation of LDTs. But this is not an accurate picture. There are numerous LDTs that perform as well as, or better than, FDA regulated tests and that yield significant benefits. In subjecting these high performing LDTs to device regulation, FDA is imposing costs without any corresponding benefit to the public health. And in imposing such costs on high performing tests, FDA would deprive laboratories of resources needed to continue to develop novel diagnostics. FDA's Proposed Rule currently ignores this reality.

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[185] Annette S. Kim et al., *supra* note 52.

[186] *See* David Dimmock et al., *supra* note 107.

4. FDA's Proposed Rule would not reduce litigation costs for laboratories.

FDA also claims that compliance with FDA regulations may reduce the incidence of litigation. In fact, subjecting laboratories to regulation as device manufacturers could potentially increase legal exposure under product liability law (although this would turn on the law of each state). For LDTs approved under PMAs, federal preemption may be available to mitigate the risks of product liability suits.[187] But according to FDA's estimates, only a small fraction of LDTs would be subject to PMA requirements. Further, there is no shortage of litigation associated with FDA-regulated devices, so there is no basis for FDA to assume FDA regulation would somehow decrease lawsuits associated with LDTs.

VI. The Proposed Rule Raises Significant Legal Concerns.

As the foregoing sections make clear, FDA should not go forward with the Proposed Rule because it is a bad policy choice. Subjecting LDTs to device law would harm the public health in numerous ways. But there is an even more fundamental reason that FDA should not go forward: finalizing the Proposed Rule would exceed the authority granted to FDA by Congress and would raise serious constitutional concerns. As discussed at the beginning of these comments, although FDA has claimed at various points over the last 30 years that it has authority to regulate LDTs as devices, it has never exercised that claimed authority in a comprehensive manner in the 85 years it had authority over devices. Instead, clinical laboratories developing LDTs have been regulated under a separate statutory and regulatory regime – CLIA – and complementary state laws. FDA is steering out of its lane in attempting to exercise jurisdiction over LDTs, with dangerous consequences for the public health.

A. LDTs are not "devices" under the FDCA.

In enacting the FDCA, Congress provided FDA with authority to regulate discrete categories of products. Each category of products – whether it be drugs, biologics, devices, or other product types – is subject to specific statutory definition. As explained below, LDTs are not devices according to the plain text of the FDCA. That conclusion is confirmed by the legislative history of the FDCA, which shows that Congress rejected a more expansive definition of the term, and by Congress's later enactment of CLIA, which established a regulatory framework for laboratories that develop and perform LDTs, and pursuant to which laboratories have been operating for 35 years (55 for laboratories subject to the original Clinical Laboratory Improvement Act of 1967). Furthermore, other provisions of the FDCA and FDA regulations confirm that LDTs do not become devices simply because they use devices. If Congress intended to provide FDA with authority to regulate LDTs as devices under the FDCA, it would have done so clearly.

1. LDTs are not "devices" according to the plain text of the FDCA.

Categorizing LDTs as "devices" would be inconsistent with the FDCA's plain text because LDTs are not physical objects. Under FDCA § 201(h), the definition of "device" comprises only physical objects, including "[a]n instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is … intended for use in the diagnosis of disease or other conditions". LDTs are not physical

[187] *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008).

objects. LDTs are methods of using various tools and devices to derive information relevant to a treatment decision to be made by a medical professional and patient. FDA's repeated insistence that an LDT is a device reflects a deep and fundamental misunderstanding of the nature of LDTs, as we described in depth earlier in these comments.

FDA's contention that an LDT is an "apparatus," "contrivance," or "article" that is "similar or related to" "instrument[s]" and "*in vitro* reagent[s]," 88 FR 68,017, cannot be squared with the fact that LDTs are not particular material things (or simply particular combinations of material things), but rather are services. Canons of statutory construction dictate that "words grouped together in a list should be given related meaning." *Dole v. United Steelworkers of Am.*, 494 U.S. 26, 36 (1990). Here, in common usage, the other terms listed in the definition of "devices" (instrument, implement, machine, implant, *in vitro* reagent) are all tangible objects, and thus the terms "apparatus" and "contrivance" should likewise be given that meaning. This conclusion is bolstered by the term "article" as a catch-all at the end of the list. The Oxford English Dictionary defines "article" as a "particular material thing, esp. one belonging to a specified class; a commodity; an item of goods or property." *Article*, oed.com, https://www.oed.com/dictionary/article_n?tab=meaning_and_use#38461235 (last visited November 6, 2023). Consistent with this definition, courts have consistently construed the term "article" to mean "material things. *See, e.g.*, *ClearCorrect Operating, LLC v. Int'l Trade Comm'n*, 810 F.3d 1283, 1291 (Fed. Cir. 2015) (construing the term "articles," in accordance with its "ordinary or natural meaning," in the Tariff Act to mean material things, and thus the term did not cover electronically transmitted digital data); *ClearCorrect Operating, LLC v. Int'l Trade Comm'n*, 819 F.3d 1334, 1336-37 (Fed. Cir. 2016) (finding the panel majority was correct in interpreting the word "articles" in section 337 to mean "material things" where that interpretation is mandated by the plain meaning of the word, the context of the statute and entire statutory scheme, and the legislative history).

The conclusion that "devices" include only physical products is consistent with the many other provisions of the FDCA that require the presence of an object, e.g., shipment and receipt in interstate commerce, commercial distribution, and holding for sale. Other provisions of the FDCA discuss devices in ways that only make sense if applied to physical products, like the requirement to repair, replace, or refund the purchase price of a device under section 518(b). The frequency of such statutory references is a powerful confirmation that Congress understood "devices" to encompass only tangible products and not intangible professional services. Several of FDA's promulgated regulations for devices similarly can only be understood when applied to a tangible product. Unlike devices, LDTs cannot be packaged or affixed with a label that bears a unique device identifier. *See* 21 CFR Part 801. Additionally, FDA's quality system regulation defines the word "product" to include "in-process devices, finished devices, and returned devices." 21 CFR § 820.3(r). Clinical laboratories may use articles to develop and perform LDTs, but that does not transform LDTs into articles themselves.

Moreover, the term "*in vitro* reagent" does not include LDTs because an LDT is not an *in vitro* reagent. An *in vitro* reagent is a chemical or mixture used to elicit a chemical reaction. *See, e.g.* 21 CFR §§ 809.10(a) (requiring the label of an IVD that is a "reagent" to include its name, "quantity, proportion or concentration", as well as "storage instructions adequate to protect the stability of the product," and "a declaration of the net quantity of contents"); 809.10(d) (describing the labeling for "general purpose laboratory reagents (e.g., hydrochloric acid)"); 809.10(e) (describing the labeling for "analyte specific reagents (e.g., monoclonal antibodies, deoxyribonucleic acid (DNA) probes, viral antigens, ligands)"). *In vitro* reagents are one component used in diagnostic tests, but they are not the tests themselves. The fact that Congress gave FDA authority over one

discrete article used to perform an LDT does not equate to Congress giving FDA authority over LDTs themselves.

Finally, LDTs did not become devices just because they have become more sophisticated. FDA asserts in the Proposed Rule that regulation is justified because LDTs have become more complex and are used to screen or diagnose complex and important medical conditions. However, FDA cannot justify applying device regulation to LDTs that are not within FDA's jurisdiction for devices. If FDA believes that any market changes could justify regulation of some LDTs but not others, then the burden is on the Agency to explain why those changes make a difference under the statute, i.e., why those changes mean that certain LDTs are devices, as defined in the FDCA. LDTs do not meet the definition of a device, and the fact that modern LDTs have become more advanced or that LDTs screen/diagnose important diseases does nothing to change that conclusion.

2. The legislative history of the Medical Device Amendments and CLIA confirm that LDTs are not "devices" under the FDCA.

Because the text of the FDCA makes it clear that LDTs are not devices, it is not necessary to consider legislative history. *See, e.g., Mohamad v. Palestinian Auth.*, 566 U.S. 449, 458-59 (2012). Nevertheless, in this situation, the legislative history of the FDCA and CLIA only strengthens the conclusion that LDTs are not devices.

a) Congress rejected a broader definition of "device" when enacting the MDA.

The legislative history of the Medical Device Amendments of 1976 (MDA) is consistent with the reading that devices are physical objects and, accordingly, do not include LDTs. Congress's Conference Report on the bill refers to devices as "products" and "articles." H.R. Rep. No. 94-1090, at 62, 65 (1976) (Conf. Rep.). The House Report also refers to devices as "products," "machines," and "articles." H.R. Rep. No. 94-853, at 6 (1976). Moreover, the House Report notes that, "generally the term 'device' is used in the bill to refer to an individual product or to a type or class of products," except where one device is indicated for multiple intended uses. *Id.* at 14. Finally, the Senate Report stated that the bill carefully defined "device" so as to specifically include implants, *in vitro* diagnostic products, and other similar or related articles. S. Rep. No. 94-33, at 17 (1975). FDA points to the use of the term "diagnostic service" in a Senate Report that accompanied an earlier iteration of the bill, *see* 88 Fed. Reg. 68,018, but what Congress referred to as "devices" were "diagnostic products," and the "device" described in the example discussed by the Report was a "diagnostic machine, the 'Radioscope.'" S. Rep. No. 93-670, at 3–4 (1974) ("One popular area for quack devices has been ***diagnostic products***. During the 1950's, the biggest source of ***such devices*** was the Electronic Medical Foundation of San Francisco.... There were estimated to be about 5,000 of the ***devices*** [a diagnostic machine called the Radioscope] throughout the country.... The blood-spotted paper was put into a slot of the electrical ***device*** called the 'Radioscope' while the operator stroked with a wand the abdomen of a person holding metal plates connected to the ***device***.") (emphasis added).

In adopting the definition of "device" at section 201(h) that is limited to articles, Congress rejected a more expansive definition that would have included "systems." As FDA points out in the preamble to the Proposed Rule, the regulations for "in vitro diagnostic product" at 21 CFR Part 809 refer to such products as "systems" and "test systems," and FDA repeatedly asserts that LDTs are "devices" because they are "test systems." 88 FR 68,017–19. But these regulations for *in vitro* diagnostic products, and particularly the definition of *in vitro* diagnostic product at 21 CFR § 809.3, were promulgated before the 1976 Medical Device Amendments. Reorganization, Republication and Recodification, *Title 21—Food and Drugs, Chapter I—Food and Drug Administration, Department*

of Health, Education, and Welfare, Subchapter H—Medical Devices, 41 Fed. Reg. 6896 (Feb. 13, 1976) (making a nonsubstantive change to reorganize and move the definition of "in vitro diagnostic product" from 21 CFR 328.3 to 21 CFR 809.3, prior to enactment of the Medical Device Amendments on May 28, 1976). And when the MDA was enacted, "device" was defined to include neither the term "test system" nor "system." Congress did not adopt that wording in 1976 or at any time since, further buttressing the fact that FDA's reliance on that regulation or the concept of a "test system" is misplaced.

FDA also has previously asserted that the addition of "*in vitro* reagents" into § 201(h) was intended to capture LDTs, but that is not so. *See* FDA, *Draft Guidance: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)*, at 5 (Oct. 3, 2014). As an initial matter, as explained above, an LDT is not an *in vitro* reagent. Moreover, the legislative history of the MDA makes clear that the addition of items to the list of articles qualifying as devices—including *in vitro* reagents—did not expand the device definition beyond tangible articles. The House Report explains that "[t]he new definition retains (in somewhat more precise detail) provisions of existing law that a device is an article or component thereof," while making changes to distinguish drugs and devices by reference to chemical action and metabolism. H.R. Rep. No. 94-853, at 14.

b) Congress's subsequent enactment of CLIA confirms that LDTs are not "devices" under the FDCA.

Twelve years after Congress established FDA's device authority in the MDA, Congress passed the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which strengthened and transformed the regulatory scheme applicable to clinical laboratories, including those performing LDTs. Neither CLIA nor its legislative history acknowledges any then-existing FDA authority to regulate LDTs. The enactment of CLIA was driven in part by the desire for greater oversight over Pap testing, which was performed entirely by LDTs. *See* H.R. Rep. No. 100-899, at 16 ("Evidence was presented to the Committee that, in many laboratories, high numbers of false negative results were being reported. At the least, women have been given a false sense of security and discouraged from seeking proper care."). Sen. Rep. No. 100-561 at 5 ("Screening for cervical cancer through use of the Pap smear is the most common type of cytological examination. ... Unfortunately, there is much evidence of seriously inadequate performance by laboratories doing cytological testing."). At the time, FDA had not cleared or approved any devices for Pap tests to screen women for cervical cancer. However, there was no discussion of FDA oversight for Pap tests or cervical cancer screening in the legislative history of CLIA. Nor were there any Congressional inquiries into FDA regarding a derogation of its responsibilities regarding such tests. Surely, if regulation of LDTs, such as Pap tests, were an FDA responsibility, there would have been an outcry that FDA had abdicated its responsibility to protect the public health. In stark contrast, FDA's responsibility to regulate LDTs was not mentioned at all. What is more, the House Report stated that laboratories "were governed by two separate and distinct statutes, Medicare and CLIA"—not the FDCA—and the Report's section on the "Current Regulatory System" does not even mention FDA. H.R. Rep. No. 100-899, at 11-12 (1988).

Moreover, in enacting CLIA, Congress established a set of detailed requirements for laboratories that are entirely separate from the FDCA's requirements for device manufacturers. For example, rather than requiring clinical laboratories to register and list under FDCA § 510(c), laboratories must obtain a certificate prior to soliciting or accepting specimens for laboratory examinations or procedures under PHSA § 353(b). In addition, rather than requiring clinical laboratories to comply with good manufacturing practices (GMP) or the quality system regulation

(QSR) to ensure that LDTs are valid and reliable, CLIA requires laboratories to: (1) maintain adequate quality control and quality assurance programs to assure the "validity and reliability" of the tests and "the proper collection, transportation, and storage of specimens and the reporting of results," PHSA § 353(f)(1)(A); and (2) participate in regular proficiency testing, PHSA § 353(f)(1)(D) & (f)(3). CLIA also established a framework according to which states could enact their own clinical laboratory laws, and if such laws were "equal to or more stringent" than the requirements under CLIA, clinical laboratories in such state could be exempt from CLIA. 42 U.S.C. § 263a(p)(2). Two states have obtained such CLIA-exempt status—Washington and New York—and one of those states (New York) expressly reviews and approves LDTs.

Furthermore, CMS regulations expressly distinguish between laboratory tests that are cleared or approved by the FDA and those that are not. Under 42 C.F.R. § 493.1253(b)(2), laboratories must establish performance specifications prior to reporting results from a "modifie[d] … FDA-cleared or approved test system, or … a test system ***not subject to FDA clearance or approval*** (including ***methods*** developed in-house and standardized ***methods*** such as text book procedures) …" (emphasis added). These performance specifications include accuracy, precision, analytical sensitivity, analytical specificity to include interfering substances, reportable range of test results for the test system, reference intervals (normal values), and any other performance characteristic required for test performance. 42 C.F.R. § 493.1253(b)(2). CMS's recognition that there are "test system[s] not subject to FDA clearance or approval" is fully consistent with Congress's understanding in enacting CLIA that such test systems were not "devices" regulated by FDA.

Because Congress did not consider FDA as having authority to regulate laboratories, applying FDA authorities in addition to CLIA would introduce inconsistencies into the regulation of LDTs. FDA promotional requirements restrict the information that a device manufacturer can share about a regulated device. *See, e.g.*, 21 C.F.R. § 801.6 (misleading statements); 21 C.F.R. § 807.97 (misbranding by reference to premarket notification). However, CLIA requires laboratories to offer consultation on interpreting test results for specific patient conditions. *See* 42 CFR § 493.1445(e)(9) (requiring the laboratory director to "[e]nsure that consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific patient conditions"). Likewise, FDA requires a manufacturer to obtain approval or clearance for labeling changes to devices, but CLIA requires laboratories to provide pertinent updates on testing information as soon as it is available. *See* 42 CFR § 493.1291(e) ("Pertinent updates on testing information must be provided to clients whenever changes occur that affect the test results or interpretation of test results."). The CLIA requirements that permit licensed pathologists to share interpretive and off-label information regarding tests performed in their laboratories is consistent with the right of such pathologists to practice medicine within the scope of their licenses. FDA restrictions on providing such interpretive and off-label information, on the other hand, would limit such pathologists' ability to practice medicine within the scope of their licenses.

Congress's enactment of a regulatory structure for clinical laboratories that is inconsistent with FDA regulation of LDTs as devices precludes FDA from asserting jurisdiction over LDTs. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125–26 (2000).[188]

[188] In addition to enacting a different regulatory scheme for laboratories and LDTs in CLIA, Congress has established reimbursement systems for diagnostic tests that results in coverage and payment for tests that are (continued…)

3. LDTs do not become devices because they use devices.

LDTs do not become devices just because devices are used in performing an LDT. This is recognized in FDA regulations. Specifically, FDA regulations do not require a person providing a service with a device to be the manufacturer of the device, and therefore, no premarket review is required for the device used by the person. For example, 21 C.F.R. § 807.65(i) exempts from registration "[p]ersons … whose major responsibility is to render a service necessary to provide the consumer (i.e., patient, physician, layman, etc.) with … the benefits to be derived from the use of a device; for example, a … clinical laboratory … whose primary responsibility to the ultimate consumer is to … provide a service through the use of a previously manufactured device." Under section 510(k) of the FDCA and 21 C.F.R. § 807.81(a), FDA's premarket requirements apply only to "[e]ach person who is required to register" an establishment. Because clinical laboratories are not required to register, they are not required to submit premarket notifications for the testing services they offer. Thus, FDA's regulatory framework already recognizes that services performed with devices are not themselves devices.

B. Had Congress provided FDA with authority over LDTs, it would have done so expressly.

Under the "major questions doctrine," as recently cemented by the Supreme Court in *West Virginia v. EPA*, 142 S. Ct. 2587 (2022), courts require "something more than a merely plausible textual basis" when an agency asserts "sweeping and consequential authority." *Id.* at 2608–09. The seminal "major questions" case is *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000), where the Court rejected FDA's claim that its "drug" and "device" authority gave it the power to regulate tobacco products, concluding that "Congress could not have intended to delegate [authority] of such economic and political significance … in so cryptic a fashion." *Id.* at 160. The Court also reasoned that "FDCA's overall regulatory scheme," "subsequent tobacco-specific legislation," and Congress's rejection of legislative proposals to give the FDA jurisdiction over tobacco all indicated that the FDA was precluded from regulating tobacco products. *Id.* at 159–61.

LDTs represent a longstanding, significant part of the U.S. healthcare system and play a critical role in delivering dynamic healthcare solutions to patients. Yet with no express statutory authorization, FDA has proposed to regulate this important sector in a manner that would fundamentally alter the market. As in *Brown & Williamson*, it is implausible that Congress chose to delegate to FDA an issue of "such economic and political significance … in so cryptic a fashion." 529 U.S. at 160. The Supreme Court has recently and repeatedly counseled that federal agencies should "hesitate before concluding that Congress meant to confer [rulemaking] authority" regarding issues of vast "economic and political significance" where the statutory basis for such a regulatory action is unclear. *See West Virginia v. EPA*, 142 S. Ct. 2587, 2595 (2022); *King v. Burwell*, 576 U.S. 473, 485–86 (2015); *Utility Air Reg. Grp. v. EPA*, 573 U.S. 302, 324 (2014). The Proposed Rule runs directly contrary to that admonition. FDA relies on a strained interpretation of "device" that is not grounded in text or legislative history and that would have major consequences, not only economically but also

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not subject to FDA clearance or approval. For example, for local coverage determinations for molecular diagnostic tests, in several regions across the country, CMS relies on Palmetto GBA's MolDX Program to determine coverage for both LDTs and for FDA-cleared or -approved tests. Also, Sec. 216 of the Protecting Access to Medicare Act, which established a new payment system for laboratory tests, defines an "advanced diagnostic laboratory test" to include a test that is neither approved nor cleared by FDA. *See* 42 U.S.C. § 1395m-1(d)(5).

for health care across the United States. The definition of "device" was not drafted with the understanding that it could be used to regulate a service in this manner. Additionally, as in *Brown & Williamson*, the overall FDCA regulatory scheme, as detailed below at V.C-D, and subsequent legislation specific to clinical laboratories, as detailed above at V.A.2.b, evince a Congressional understanding that LDTs do not fall within the FDCA's scope. Finally, Congress has considered—and has so far declined to enact—legislation that *would* have given FDA authority to regulate LDTs. *See* H.R. 8616 – VALID Act of 2022 (117th Cong.); H.R. 4128 – VALID Act of 2021 (117th Cong.). *See West Virginia*, 142 S. Ct. at 2614. Given its lack of statutory basis, FDA should not suppose that it has the power to regulate LDTs in this manner.

C. LDTs cannot be subject to any FDCA authorities that require devices to be introduced or delivered into interstate commerce for commercial distribution.

Looking beyond the FDCA's "device" definition to other provisions of the statute confirms that the FDCA's device authorities clearly were not intended to cover LDTs. To start with, many of FDA's authorities to regulate devices require that devices be introduced or delivered for introduction into interstate commerce for commercial distribution. *See, e.g.*, FDCA §§ 510(k) ("Each person who is required to register under this section and who proposes to begin the *introduction or delivery for introduction* into interstate commerce *for commercial distribution* of a device intended for human use shall, at least ninety days *before making such introduction or delivery*, report to the Secretary … action taken by such person to comply with requirements under section 514 [related to performance standards] or 515 [related to premarket approval] which are applicable to the device.") (emphasis added); 515(b)(1) (explaining that the Secretary must require premarket approval when a class III device "was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976," "is of a type so introduced or delivered," and "is substantially equivalent to another device within that type[.]"); 518(a)(1) (triggering notification requirements when the Secretary determines that, among other things, "a device intended for human use which is introduced or delivered for introduction into interstate commerce for commercial distribution presents an unreasonable risk of substantial harm to the public health[.]"). But LDTs are not, and indeed cannot be, introduced or delivered for introduction into interstate commerce for commercial distribution.

The FDCA defines "interstate commerce" as "(1) commerce between any State or Territory and any place outside thereof, and (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body." 21 U.S.C. § 321(b). But "[t]he typical LDT … never physically leaves the laboratory. There is no 'introduction' and no 'delivery.'"[189] That is because LDTs are "intended for clinical use and designed … [to be] used within a single laboratory[.]" Citizen Petition Denial Response from FDA CDRH to ACLA re: Docket No. FDA-2013-P-0667 at 1 (July 31, 2014) (hereinafter "FDA CP Response"). For this basic structural reason, an LDT being performed cannot logically be considered commerce between any state or territory.

Even if LDTs are introduced or delivered for introduction into interstate commerce, they are not introduced for "commercial distribution." "Commercial distribution" is defined under 21 C.F.R. § 807.3(b) to mean "any distribution of a device intended for human use which is held or offered for sale," and excludes "[i]nternal or interplant transfer of a device between establishments within the

[189] Charrow Memorandum, *supra* note 35, at 9.

same parent, subsidiary, and/or affiliate company." In a Compliance Policy Guide (CPG), FDA interpreted commercial distribution to require delivery of the device to purchasers or consignees. FDA, CPG § 300.600 ("Commercial Distribution with Regard to Premarket Notification (Section 510(k))") (1978, reissued 1987). Specifically, under this CPG, FDA will consider a device in commercial distribution *without* delivery only if the manufacturer can establish that, among other things, it had accepted or been prepared to accept at least one purchase order before enactment of the MDA "generally *with delivery to occur* immediately or at a promised future date." *Id*. (emphasis added). Thus, FDA has interpreted "commercial distribution" to mean that, at the very least, delivery of the device is anticipated. And notably, a court has upheld this CPG's interpretation of "commercial distribution." *U.S. v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, 993-95 (W.D. Mich. 1985). In *An Article of Device Consisting of 1,217 Cardboard Boxes*, the court cites CPG 7124.26, which contains identical language regarding delivery of the device, stating such CPG was "the current expression of the [FDA's] interpretation of 'commercial distribution,'" as well as a letter from FDA in which the Agency explained that the requirements for "commercial distribution" would be satisfied if there were "adequate documentation of separate, specially labeled *packaging*, and at least one sale prior to May 28, 1976" (emphasis added). The court then concluded that the explanation in the letter, "together with the agency's compliance policy guide 7124.26, is a reasonable interpretation of the phrase 'commercial distribution'." *Id.* at 994-95.

FDA contends that "commercial distribution" "does *not* require the physical transfer of an object" but only that a device be "on the market." 88 Fed. Reg. 68,021. But that gloss ignores FDA's longstanding interpretation of "commercial distribution," which requires actual or anticipated *delivery*.

For these reasons, LDTs cannot be subject to any FDCA authority that requires introduction or delivery into interstate commerce for commercial distribution. This includes FDA's premarket review requirements under FDCA § 510(k), among many other provisions. This statutory context confirms that LDTs fall outside the scope of "devices." Other provisions of the FDCA also discuss "devices" in ways that only make sense if applied to physical objects. *See, e.g.*, FDCA §§ 513(a)(2)(B) ("labeling" for devices); 514(a)(2)(C) ("labeling for the proper installation, maintenance, operation, and use" of a device); 519(f) (labels that "bear a unique identifier" so that a device can be tracked); 515(c)(1)(C) ("the manufacture, processing, and, when relevant, packing and installation of" a device); 518(b) (requiring a "manufacturer, importer, distributor, or retailer" of a device to "repair," "replace," or "refund the purchase price").

In response to this argument, FDA offers a blithe retort that such tests would then just have to go through the PMA or De Novo pathway. This conclusion—that a device not subject to section 510(k) is independently subject to section 515 or 513(f)(2) of the FDCA—is not supported by the text of the FDCA or FDA's own interpretation of the statute. Rather, submission of a premarket application under section 515 or a De Novo request under section 513(f)(2) *satisfies* the requirement to submit a 510(k) premarket notification, which generally applies to all devices unless subject to a specific exemption.

Specifically, section 510(k) of the FDCA requires a premarket notification prior to introduction of "a device," not a device that is not otherwise subject to premarket approval requirements, De Novo classification requirements, investigational device exemption, or that is otherwise 510(k) exempt. The 510(k) requirement thus applies broadly across all devices, but exemptions from the 510(k) requirements have been added to the FDCA (e.g., for certain class I and

II devices, under section 510(*l*) and (m), and for investigational devices under section 520(g)), or established by FDA through regulation based on its interpretation of the FDCA.

With regard to PMA applications and De Novo classification requests, FDA has interpreted the statute such that a PMA application under section 515 or a De Novo classification request under section 513(f)(2) satisfies the requirement for a premarket notification under section 510(k). In its 1976 proposed rule establishing the Part 807 regulations for premarket notifications, the Agency explained that "[a] premarket notification under § 807.81 is not required for a device for which a premarket application under section 515 of the act, or for which a petition to reclassify from class III to class I or II under section 513(f)(2) of the act, is pending before FDA. For such devices, the other submissions will serve the purpose of a notification under section 510(k) of the act." Proposed Rule, Establishment Registration and Premarket Notification Procedures, 41 Fed. Reg. 37458, 37460 (Sept. 3, 1976). In the final rule establishing such regulations, FDA confirmed this interpretation, explaining that "[i]f a premarket approval application has been submitted, a premarket notification submission would not be required since FDA would already be advised of the intent to market." See Final Rule, Establishment Registration and Premarket Notification Procedures, 42 Fed. Reg. 45250, 42523 (Aug. 23, 1977) (emphasis added).

Moreover, even if FDA were right that LDTs would need to resort to the PMA or De Novo pathway (which it is not), this argument ignores a more fundamental point: it defies logic that Congress would create a system to regulate LDTs where foundational provisions would not apply. By FDA's own estimates, some 80% of LDTs that require premarket review would be subject to the 510(k) premarket notification process. The fact that the principal pathway to market for devices (not to mention other aspects of the FDCA) would be unavailable to LDTs is further evidence that the device regulatory framework was never intended to reach LDTs. This argument also would further undermine FDA's estimate of the costs associated with the Proposed Rule, as the tens of thousands of LDTs that FDA had estimated to be eligible for the 510(k) pathway would be subject to the lengthier, more expensive PMA and De Novo pathways.

D. LDTs are not "held for sale" as required under FDCA Section 301(k).

As an additional basis, FDA has asserted that it may regulate LDTs under Section 301(k) of the FDCA by claiming that LDTs are "held for sale." This argument fails under a commonsense reading of Section 301(k) and applicable case law.

Under 301(k), the following acts are prohibited: "The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, if such act is done while such article is *held for sale* (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded." 21 U.S.C. § 331.

As an initial matter, LDTs are not "article[s]" "held for sale." A physician's test order for an LDT service is satisfied by the laboratory performing in-house testing services and reporting back to the ordering physician the result of that service, not by the laboratory transferring title to and possession of the testing methodology or protocol to the ordering physician as a third-party purchaser.

This view comports with the case law, which extends FDA's jurisdiction to regulate drugs and devices after release by the original manufacturer, but only insofar as such regulated products are

being delivered or transferred to another ultimate consumer. In this regard, *U.S. v. Regenerative Sciences, LLC*, 741 F.3d 1314 (D.C. Cir. 2014), is inapplicable to LDTs. In *Regenerative Sciences*, the court stated that a drug—doxycycline—was adulterated when mixed with cells from patients, and then such drug-cell mixture was held for sale when administered to a patient for treatment. This does not occur with LDTs, however, which by definition are not transferred to anyone, but performed by the developer. Thus, LDTs are not "held for sale." For example, "held for sale" does not include use of a device to facilitate the work of a healthcare professional where that device is not transferred to the patient. *See Shahinian v. Kimberly-Clark Corporation*, No. 14-CV-8390, 2017 WL 11595343 (C.D. Cal. Mar. 7, 2017) (holding surgical gowns were not "held for sale" because they "were bought for the use of [the] hospital staff, the 'ultimate consumer' of the product").

In cases cited by FDA in its Citizens Petition Denial Response and by HHS in the Charrow Memorandum, the regulated drug or device product was delivered or transferred from one party (typically a doctor) *to* an ultimate consumer (typically a patient). *See* Citizen Petition Denial Response from FDA Center for Devices and Radiological Health to ACLA re: Docket No. FDA-2013-P-0667 at 1 (July 31, 2014); *United States v. Cassaro, Inc.*, 443 F.2d 153, 156 (1st Cir. 1971) (citing *Hipolite Egg Co. v. United States*, 220 U.S. 45, 54 (1911), for the proposition that the "held for sale" standard of section 301(k) has long been afforded a liberal reading, encompassing "[a]ll articles, compound or single, not intended for consumption by the producer"); *United States v. Sullivan*, 332 U.S. 689, 697 (1948) (cited for the proposition that section 301(k)'s "held for sale" requirement is "designed … to extend the [FDCA's] coverage to every article that had gone through interstate commerce until it finally reached the ultimate consumer"); *see also United States v. Evers*, 643 F.2d 1043, 1050 (5th Cir. 1981) (summarized by FDA as "stating that physicians holding drugs for use in their practice may be considered to hold them for sale within the meaning of section 301(k) of the FDCA," and where such drugs were delivered to an ultimate consumer, i.e., the patient); *United States v. Diapulse Corp. of Am.*, 514 F.2d 1097, 1098 (2d Cir. 1975) (which FDA quoted for the proposition that "devices, used in the treatment of patients, may properly be considered 'held for sale' within the meaning of the Food, Drug, and Cosmetic Act," and where the device at issue was administered to patient); *United States v. Rhody Dairy, L.L.C.*, 812 F. Supp. 2d 1239 (E.D. Wash. 2011) (holding that drugs are "held for sale" when they are administered); *United States v. Torigan Labs., Inc.*, 577 F. Supp. 1514, 1521 (E.D.N.Y. 1984) ("All articles held for purposes other than personal consumption—whether to be sold or given away—are deemed to be held for sale under the Act."); *Articles of Animal Drug Containing Diethylstilbestrol*, 528 F. Supp. 202, 205 (D. Neb. 1981) ("This Court subscribes the view that an article of drug or device is "held for sale" if it is used for any purpose other than personal consumption."). This does *not* occur with LDTs, or any component of an LDT. Only the test report, which includes *patient-specific information* yielded from performance of an LDT, is transferred back to the ordering physician, and a test report is not a device.

Even if LDTs were "held for sale," section 301(k) only applies while LDTs are "held for sale … after shipment" in interstate commerce. By definition, LDTs are never shipped in interstate commerce. They are performed only within the laboratory in which they are developed. To the extent that the methods for performing LDT services are transferred *anywhere*, it is between laboratories under common ownership and control, which then independently validate such methods. This is not "interstate commerce," as reflected by its exclusion from the definition of "commercial distribution." 21 CFR § 807.3(b).

E. Imposing device law on LDTs would violate the First Amendment.

The FDA's proposal to regulate LDTs—that is, to regulate intangible methodologies, as opposed to the manufacture and sale of physical articles, and the communications between

laboratory directors, clinical consultants, and ordering providers—raises serious constitutional concerns.

The design and execution of LDTs, as well as the communication of test reports to healthcare providers, inherently involves constitutionally protected speech. As explained earlier in these comments, the responsibilities of a high-complexity laboratory director and clinical consultant include ensuring that reports of test results include pertinent information required for interpretation and consulting with the ordering physician (or other health care professional) regarding the appropriateness of the testing ordered and the interpretation of test results. 42 CFR §§ 493.1445 & 439.1457. Accordingly, laboratory directors and clinical consultants are required to share information regarding clinical meaning of analytical test results, including their viewpoints on the meaning of that information for a particular patient. In this way, laboratories act as providers of health care services and are meaningfully different than device (or drug) manufacturers that principally make promotional claims about products and do not provide similar clinical care services.

However, FDA regulation of LDTs as medical devices would necessarily chill this speech. Turning laboratories into medical device manufacturers would restrict speech because device manufacturers and their employees are limited to communicating information that is "on-label," i.e., consistent with the approved or cleared labeling of a device. Accordingly, laboratory directors and clinical consultants would be restricted from sharing any information about the meaning of a test result if FDA has not authorized that speech.

To the extent that FDA would regulate speech about the interpretation of test reports based on its content (for example, limiting test report statements, or statements made during a clinical consultation, regarding the effect of a patient's genetic makeup on drug response until FDA has reviewed or approved such statements) or viewpoint (for example, limiting expression in a test report, or during a clinical consultation, of a view that is a matter of scientific debate, such as the relative importance of a particular biomarker to diagnosing a particular disease), strict scrutiny, or at a minimum heightened scrutiny, applies. *See NIFLA v. Becerra*, 138 S. Ct. 2361, 2371–75 (2018) (speech by professionals is not exempt from the rule that content-based regulations of speech are subject to strict scrutiny); *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 565 (2011) (heightened scrutiny applied to regulation of speech in aid of pharmaceutical marketing). Strict scrutiny properly applies to such speech because it does not propose a commercial transaction and is not an advertisement or otherwise clearly commercial. *See Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 66–67 (1983).

Even under the less stringent standards applicable to commercial speech, FDA would be hard-pressed to justify its restrictions because FDA could achieve its stated goals through alternative, less-intrusive means. Under *Central Hudson Gas Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557 (1980), a three-part test applies to determine whether a restriction on lawful and not misleading commercial speech is permissible: (1) the asserted governmental interest must be substantial, (2) the regulation must be in proportion to that interest, and (3) the regulation must be designed carefully to achieve the government's goal. *Central Hudson*, 447 U.S. at 564. Here, although FDA asserts a general concern about unreliable LDTs, it does not identify a particular substantial governmental interest in controlling what non-misleading information may be communicated in a test report. *See Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 197, 225–27 (S.D.N.Y. 2015). The FDA is also unlikely to be able to show that "the regulatory technique" proposed (that is, the application of speech-limiting "device" regulations to LDTs) is in proportion to whatever substantial "interest" it may have. *Central Hudson*, 447 U.S. at 564. The FDA has an interest in ensuring that *misleading* information is not communicated in a test report, but requiring burdensome FDA approval or clearance of *any* change in reporting suppresses far more expression than would serve the FDA's

interest. *See id.* at 565. Finally, in this dynamic, cutting-edge industry, there is a serious risk that regulating LDTs as devices would undermine the goal of ensuring that appropriate information is conveyed to providers in connection with the tests they order. As the CLIA regime recognizes, clinical laboratories should be able to provide pertinent updates on testing information as soon as it is available. FDA regulation of LDTs as devices would prevent that expression.

F. FDA regulation would interfere with the practice of medicine.

Laboratories employ licensed pathologists, genetic and clinical counselors, and other licensed medical professionals, and these professionals are an integral part of patients' medical teams. As explained in section II.B, above, the laboratory director is responsible for ensuring that selected test methodologies "have the capability of providing the quality of results required for patient care," "reports of test results include pertinent information required for interpretation," and "consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific conditions." 42 CFR § 493.1445(e)(3)(i), (e)(8) - (e)(9). The laboratory also must be staffed with someone who qualifies as a clinical consultant, who is expressly responsible for "provid[ing] consultation regarding the appropriateness of the testing ordered and interpretation of test results." *Id.* § 493.1457.

In practice, many clinical laboratories have entire medical teams dedicated to these functions, which include the application of medical judgment when interpreting test results, annotating test reports, and consulting with the patient's care team. Regulating laboratories as device manufacturers would restrict the ability of these medical professionals to fully express their medical judgment, which may include the practice of medicine as recognized by law in some states. *See, e.g.*, Utah Code Ann. §§ 58-67-102(19)(a) ("Practice of medicine" means "(i) to diagnose ... by any means or instrumentality") & 58-67-102(12)(a) ("Diagnose" means "to examine in any manner another person, parts of a person's body, substances, fluids, or materials excreted, taken, or removed form a person's body, or produced by a person's body, to determine the source, nature, kind, or extent of a disease or other physical or mental condition"). In particular, the attendant restrictions on providing interpretations or off-label information would interfere with their ability to appropriately consult with ordering physicians. FDA is prohibited, however, from regulating the practice of medicine under section 1006 of the FDCA. *See also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001) (FDA's "mission [is] to regulate ... without directly interfering with the practice of medicine.")

G. The NPRM Fails to Comply with Section 553(b) of the Administrative Procedure Act.

As amended by the Providing Accountability through Transparency Act of 2023, Section 553(b) of the Administrative Procedure Act requires that a Notice of Proposed Rulemaking include "the Internet address of a summary of not more than 100 words in length of the proposed rule, in plain language, that shall be posted on the Internet website under section 206(d) of the E-Government Act of 2002 (44 U.S.C. 3501 note) (commonly known as regulations.gov)." 5 U.S.C. § 553(b)(4). The NPRM fails to comply with this requirement, as it does not include the Internet address at which such a summary may be found, nor does the rulemaking docket for the Proposed Rule at regulations.gov include any summary of the rule, much less "summary of not more than 100 words in length of the proposed rule, in plain language."

That omission undermines the ability of stakeholders—particularly smaller laboratories and their employees—to understand FDA's proposal and participate meaningfully in the public comment process. Congress determined that a "plain language" summary is essential to providing

"[a]ccountability" and "[t]ransparency" in rulemaking proceedings, Pub. L. No. 118-9, § 1, and thus mandated that every "notice of proposed rulemaking … *shall* include" the required summary, 5 U.S.C. § 553(b)(4) (emphasis added). FDA accordingly must publish a concise summary of its proposal, reissue the Notice of Proposed Rulemaking with the mandatory Internet address included, and then restart this proceeding with a new public comment period.

VII. The Agency Could Revise the Rule to Reduce, but not Eliminate, the Net Negative Impact of the Rule to Public Health.

As explained in these comments, ACLA believes that FDA should not finalize the Proposed Rule. As a matter of law, the Proposed Rule exceeds FDA's authority and raises significant constitutional issues. Moreover, even if FDA had authority to move forward (which it does not), the Proposed Rule should be abandoned because it is bad policy. However, the Proposed Rule seeks comment on FDA proposals that FDA suggests could lessen the harm caused by the Proposed Rule. If FDA nonetheless decides to ignore the deficiencies set forth in these comments and proceeds in finalizing the Proposed Rule, it could adopt certain approaches to lessen the harm caused by the Proposed Rule. However, we emphasize that none of these, individually or collectively, would cure the legal or policy deficiencies identified throughout these comments, nor would they completely eliminate the net harm of the Proposed Rule such that its benefits would outweigh its costs. Nothing in the following comments should be regarded as ACLA conceding that FDA has a legal or public policy basis to proceed with this rulemaking.

A. Grandfathering for existing tests.

To reduce but not eliminate the net harm of the rule, all LDTs that are first made available prior to publication of the final rule could be subject to ongoing enforcement discretion and not be expected to comply with premarket submission requirements or quality system requirements related to design controls. This mitigation would reduce the costs for both laboratories and FDA related to the backward-looking exercise of re-validating and submitting applications for existing tests. Accordingly, it would also mitigate the harms to patients from important tests being culled from existing test menus and would lessen (but not eliminate) the need to divert existing resources currently focused on innovation and clinical testing, thus lessening the net negative impact of the rule to innovation and patient access to important tests.

Failing to grandfather existing tests from at least these portions of FDA regulation also would improperly disregard the legitimate reliance interests of clinical laboratories that offer these LDTs, as well as the interests of the patients who would otherwise benefit from tests suddenly rendered uneconomical. *See DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913-15 (2020) (failing to consider reliance interests of DACA recipients, and weigh those interests against competing concerns, was arbitrary and capricious). Those reliance interests are substantial, given FDA's decades-long policy of generally not enforcing device requirements with respect to LDTs and the countless business decisions affecting the landscape of the U.S. health care system that have been made against the backdrop of that policy.

Importantly, FDA's proposed exemptions for "1976-type" LDTs are neither adequate nor sensible to lessen the high costs to laboratories and patients in the Proposed Rule. The exemption for "1976-type" LDTs is limited only to those tests that use "manual techniques (without automation)." However, these types of tests are few and far between. Even simple laboratory tests that existed in 1976 have since been updated to leverage automated systems, such as automatic pipetting, that improve the accuracy, consistency, and quality of such tests. For example, while a

cytogenetics test *can* be performed without automated instrumentation, it is commonly performed using an automated metaphase finder to locate cells for karyotype and analysis. As another example, differential cell counts used to be performed manually by a laboratory technician performing a manual blood smear and counting cells; but now, automation lines draw the blood, prep the smear, and count the cells, with only certain abnormal findings triggering a manual review by a technician or pathologist. This extremely narrow exemption, therefore, would only encourage less accurate, less consistent, and lower quality methods of testing. Instead, FDA could further mitigate the net negative impact of the rule by exempting all LDTs that are offered prior to finalization of the rule, regardless of complexity or risk-level.

It would mitigate the net negative impact of the rule to a lesser degree to grandfather only those tests that have been previously approved by New York State—regardless of risk classification. Such tests have been evaluated for their analytical and clinical validity by a third party that FDA itself previously has relied upon for third-party reviews. However, we note that grandfathering tests approved by the state of New York would be inadequate to completely alleviate laboratories from having to cull certain tests from their menus and to prevent FDA from being overwhelmed by marketing submissions at years 3.5 and 4 of the phaseout period. This is because such a policy would not extend to laboratories outside of New York that do not offer tests nationally, e.g., local, specialty laboratories, and New York does not review and approve *all* LDTs. For example, New York does not review and approve LDTs for multi-analytic immunohistochemistry stains, which it considers to be performed by "standard methods."[190]

B. Extended implementation timeline.

The implementation timeline could be extended for all tests to reduce, but not eliminate, the net harm of the rule. Four years to phase in an ill-fitting regulatory regime is hardly appropriate given the significant amount of work that would be needed to bring activities into compliance. Even in 2014, when FDA proposed through draft guidance to phase-in device regulation of LDTs, the Agency proposed a 9-year transition period.[191] In the VALID Act, a bill for which FDA gave substantial input and which was re-introduced as recently as March 2023, a transition period of up to 10 years was available for certain tests in addition to grandfathering of all LDTs available at the time of enactment.[192] Extending the implementation timeline would enable laboratories to stretch their existing resources more efficiently compared to the implementation timeline as proposed, such that fewer personnel would need to be completely diverted away from their existing innovation/testing activities to focus on backward-looking re-validations and establishing FDA-compliant quality and postmarket systems. It would also mean that fewer new personnel would need to be hired, and, ultimately, fewer existing tests may need to be culled from test menus due to

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[190] *Test Approval*, DEP'T OF HEALTH, WADSWORTH CENTER, https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval (last visited Nov. 15, 2023).

[191] FDA, DRAFT GUIDANCE: FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOPED TESTS 26 (2014), https://www.fda.gov/media/89841/download.

[192] Press Release, Office of Congresswoman Diana Degette, *Lawmakers move to reform diagnostic testing in U.S., FDA says legislation is a 'top priority' for the agency* (Mar. 29, 2023), https://degette.house.gov/media-center/press-releases/lawmakers-move-reform-diagnostic-testing-us. Text of the bill is available here: https://degette.house.gov/sites/evo-subsites/degette.house.gov/files/evo-media-document/118-valid-act.pdf.

competing demands for limited resources that make obtaining clearance or approval for all existing tests impossible. Accordingly, this would reduce, but not eliminate, the negative impact of the rule to innovation and access to testing. Finalizing the Proposed Rule without extending the transition period would harm the reliance interests of clinical laboratories engendered by FDA's decades-long policy of generally not enforcing device requirements with respect to LDTs. *See DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913-15 (2020) (where agency is "not writing on a blank slate," it must consider reliance interests).

Additionally, FDA could further extend the implementation timeline for LDTs approved by New York State that are introduced after publication of the final rule to reduce, but not eliminate, the net harm of the rule. As discussed above, New York State evaluates the analytical and clinical validity of LDTs, and extending the transition period for these tests would be consistent with the recognition that they have already been evaluated by a third party for analytical and clinical validity. In addition to the reduced harm to laboratories and patients that would accrue from a longer implementation timeline, this would also lessen the burden to FDA of reviewing thousands of submissions submitted all at once when submissions become due. Instead, FDA could focus on those tests for which there has been no independent review and would still receive at a later date premarket submissions for tests that have received New York State approval. This was the approach adopted in VALID, where tests approved by New York State under molecular specialties would have received an additional 5 years for transition, and all other tests approved by New York State would have received an additional 2 years.

ACLA disagrees with all discriminatory applications of LDT regulation based on the type of entity offering the LDT, including but not limited to the proposal in the Proposed Rule to extend the implementation timeline only for small laboratories with revenues below a certain threshold. There is no public health basis for granting only these small laboratories a longer transition period, and doing so would be completely inconsistent with one of FDA's underlying arguments in the Proposed Rule – that the same regulatory requirements should apply to the same activities, regardless of where or by whom they are performed.

C. New York State and MolDX programs.

FDA could recognize approvals by New York State and coverage decisions by MolDX as clearances and approvals of LDTs for purposes of device regulation to reduce, but not eliminate, the net harm of the rule. As detailed above, both of these programs review LDTs for their analytical and clinical validity based on detailed technical submissions. Accordingly, FDA could reduce, but not eliminate, net harm from the rule by recognizing their decisions as satisfying the FDA requirement for clearance or approval by exercising enforcement discretion for tests that have gone through such programs, or, at minimum, structure an expedited approval/clearance pathway that would alleviate the burden of FDA re-review of such tests. Likewise, with respect to LDT clinical trial assays that New York State permits to be used for clinical management without prior approval, FDA could reduce the net harm of the rule by continuing enforcement discretion with respect to such clinical trial assays. Without leveraging these programs, by FDA's own estimate, the Agency would face an annual increase in premarket submissions of 500% for PMA Submissions, 500% for De Novos, and 80% for 510(k)s. Leveraging these programs would reduce, but not eliminate, the burden on both laboratories and FDA associated with implementation of the Proposed Rule.

D. Flexible modifications policy.

To lessen the burden on laboratories and FDA associated with premarket submissions for modifications to cleared and approved tests as discussed above, FDA could develop a flexible approach that enables laboratories to modify cleared and approved tests without premarket review.

For example, the VALID Act would have allowed CLIA-certified high-complexity laboratories or the marketing authorization holder (if not a high-complexity laboratory) to make certain modifications to an approved test without seeking independent premarket review. Modifications exempt from premarket review would have included modifications that do not (a) significantly change the indications for use, except for some changes to specimen type; (b) cause the test to no longer comply with mitigating measures or restrictions (conceptually similar, but not the same, as special controls); (c) significantly change performance claims or significantly and adversely change performance; or (d) adversely change the safety for individuals who come in contact with the test. Importantly, the VALID Act made clear that modifications to extend specimen stability would have been exempt as long as they met such requirements. And FDA still has a flexible policy for modifications by high-complexity laboratories to EUA-authorized COVID-19 tests. Under the current COVID-19 Testing Guidance, a high-complexity CLIA-certified laboratory can modify an EUA-authorized test, including one for which the laboratory does not hold the EUA, if the modifications do not change the indications for use set forth in the EUA and do not change the analyte specific reagents.[193]

A flexible policy for such modifications, established through complementary amendments to the FDCA and CLIA regulations or through continued FDA enforcement discretion, could reduce loss of availability of important tests that are modified to enhance performance and improve patient access. Specifically, FDA, CMS, and CDC could reduce but not eliminate the net harm of the rule by coordinating on complementary regulations to distinguish between modifications to cleared or approved IVDs, which would remain subject to CLIA exclusively, and novel LDTs for which FDA might require premarket review. To maximize harm reduction, this flexible modifications policy would need to extend to grandfathered tests, as well, because failure to do so would quickly render any grandfathering policy obsolete as modifications are routinely made to improve performance and adjust to changing circumstances.

The VALID Act also proposed a Technology Certification Program, under which test developers that received a technology certification order could introduce non-high-risk tests without individual tests undergoing premarket review. To be eligible to participate in the program, the developer had to have demonstrated expertise in a particular technology and a commitment to quality systems. In addition to reducing the administrative burden for non-high-risk tests, the program necessarily would have accommodated modifications to such tests. To reduce the net harm from the Proposed Rule, FDA could consider whether it could establish a similar program (as it did with the Digital Health Precertification Program) to facilitate a more flexible policy toward modifications and the introduction of new tests. To the extent that FDA believes that such a program would not be appropriate, or if FDA believes that it lacks legal authority to implement such a program, those positions should be considered and explained.

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[193] FDA, *Policy for Coronavirus Disease-2019 Tests (Revised)** at 12 (Jan. 12, 2023).

E. Enforcement discretion for low-volume tests.

FDA could continue to exercise enforcement discretion for low-volume tests, at least for the requirements for premarket review, to reduce but not eliminate the net harm of the rule. As detailed earlier, many LDTs are not used at volumes that justify the cost of a premarket submission (including PMAs, De Novo or even 510(k)). Although some of these tests are for rare diseases that would fit within the Humanitarian Device Exemption (HDE) pathway, many would not, given the extremely low HDE ceiling for patient groups that can be served by a diagnostic test under the HDE program. Other low volume tests would be used very infrequently, significantly less than the thresholds contemplated by the HDE program.

Even for those tests that would satisfy the thresholds for an HDE, the requirements and burdens associated with obtaining an HDE are not trivial, and in most cases the costs would not justify development and approval of the tests. Moreover, the HDE prohibits test developers from commercializing their assay except under narrow conditions. Given the public health contribution of these tests – and the fact that many would be abandoned if FDA proceeds with the Proposed Rule – FDA could exercise enforcement discretion from premarket requirements for low-volume LDTs to reduce the net harm of the rule. To do this, FDA could define a "low volume" test and fully explain the basis for any chosen volume limit for this category through notice and comment rulemaking.

F. Classification panels.

FDA could establish classification panels for currently available LDTs, as it did for medical devices when the MDA was enacted, to reduce the net harm of the rule. By FDA's estimates, there are 80,400 LDTs currently available that would require premarket review. Even if these tests are grandfathered, unless there is a sensible modifications policy, FDA would quickly be flooded with premarket submissions for LDTs. But clinical laboratories are not experienced at selecting predicate devices, and even if they were, there are not suitable predicate devices for all of their tests, which would force them through the more burdensome and expensive PMA or De Novo pathway. Even low-risk novel tests would have to go through the De Novo pathway. To streamline premarket submissions for LDTs, FDA could issue an RFI regarding available LDTs and classify tests so that laboratories would have more clarity on the appropriate premarket submission pathway for their new and modified tests (and existing tests, if not grandfathered).

G. CLIA regulation.

FDA could consult with CMS and CDC on an alternative approach whereby CLIA regulations are updated with appropriate additional requirements for validation of LDTs, including modifications to cleared and approved IVDs and novel LDTs. If FDA rejects this approach, it must provide a reasoned basis for doing so. A mere conclusory statement that the Proposed Rule is complementary to the CLIA regulations is not only insufficient; it is patently wrong. CLIA regulations expressly acknowledge that laboratories may "modif[y] an FDA-cleared or approved test system, or introduce a test system not subject to FDA clearance or approval,"[194] and the Proposed Rule creates a conflict between FDA's regulations and CLIA's longstanding and relied-upon regulations. CLIA also requires compliance with its own quality system regulations, requires laboratories to be inspected, and imposes fees on laboratories.

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[194] 42 CFR § 493.1253(b)(2).

H. Request for information (RFI).

As explained earlier in these comments, FDA made no attempt to collect information about the number of high-complexity CLIA laboratories or LDTs currently being offered that would be affected by the Proposed Rule, despite the Agency having the tools to do so. For example, FDA could have coordinated with other HHS agencies, CMS and CDC, to collect information from CLIA-certified laboratories regarding the number of laboratories that are high-complexity laboratories and the number of LDTs offered by each such laboratory. FDA also could have issued an RFI seeking information regarding the number of high-complexity clinical laboratories and the number and type of LDTs currently being offered.

Failing to obtain this information prior to finalizing the Proposed Rule would be irresponsible and undoubtedly maximize the harm from the rule. Accordingly, FDA could potentially mitigate, but not eliminate, the harm from this proposed rule by first issuing an RFI for information about high-complexity clinical laboratories that would be affected and the number and type of LDTs currently available, thereby increasing the likelihood that any finalized policy is informed by accurate data.

I. Equal treatment of LDT developers.

ACLA strongly believes there is no reasoned basis for exempting particular laboratories from any FDA policy regarding LDTs or otherwise singling out any category of LDT developer for disparate treatment. FDA should not go forward with the Proposed Rule with special, different rules for small laboratories, large laboratories, academic medical centers (AMCs), laboratories in particular states or locations, or other categories of test developers.

FDA requested comments specifically on whether a different policy should apply for LDTs offered by AMCs. ACLA appreciates the important role of AMCs in the health care delivery system and the scientific and clinical expertise developed within AMCs, and we recognize their contributions to clinical and medical research. However, as FDA notes in the Proposed Rule, there is no established definition of an AMC laboratory, and defining any other developer-based exemption would face similar challenges. Further, differences in expertise in test development and the quality of testing at AMCs and commercial laboratories are not supported by evidence. Additionally, there is no meaningful difference between the tests offered by AMCs and commercial laboratories. The test menus offered by large AMCs and commercial laboratories are similar.[195] In that regard, both AMCs and commercial laboratories are engaged in routine testing and in supporting care for patients with rare diseases and unique conditions. Importantly, establishing an exemption for AMCs could create negative health disparities for populations without access to an AMC.

In sum, there is no reasoned basis for treating particular test developers, including AMCs, differently than commercial laboratories, and doing so would be arbitrary and capricious in violation of the Administrative Procedure Act (APA). *See Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997) ("The disparate treatment of functionally indistinguishable products is the essence

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[195] *See, e.g.*, UCSF Health Clinical Laboratories, *UCSF Health Clinical Laboratories Test Directory*, https://www.testmenu.com/UCSFClinLab (last visited Nov. 11, 2023); Stanford Medicine, *Stanford Medicine Test Directory*, https://stanfordlab.com/content/stanfordlab/en/test-directory/search-results.html#&page=1 (last visited Nov. 11, 2023); NYU Langone Health, *NYU Langone Health Clinical Laboratories Test Directory*, https://www.testmenu.com/nyumc (last visited Nov. 11, 2023).

of the meaning of arbitrary and capricious.") (citations omitted). Indeed, failure to treat similarly situated parties similarly would be regarded as arbitrary and capricious under the APA and would provide yet another basis for a legal challenge to FDA's regulation of LDTs. *Grayscale Investments v. SEC*, 82 F. 4th 1239 (D.C. Cir. 2023); *Nasdaq Stock Market LLC v. SEC*, 38 F.4th 1126 (D.C. Cir. 2022)

CONCLUSION

For all of the reasons stated above, the Proposed Rule should be withdrawn. Rather than expending resources to finalize the Proposed Rule, if FDA seeks to establish additional oversight of LDTs, the Agency should engage with stakeholders, including ACLA, other HHS agencies, and Congress in a renewed effort to develop legislation that would establish appropriate regulatory authority for such additional oversight.

Exhibit 1: Professor Chris Carrigan, Global Economics Group, Review of the Food and Drug Administration's Preliminary Regulatory Impact Analysis for its Medical Devices; Laboratory Developed Tests Proposed Rule

Review of the Food and Drug Administration's Preliminary Regulatory Impact Analysis for its Medical Devices; Laboratory Developed Tests Proposed Rule

Christopher Carrigan[1]

December 4, 2023

[1] I am Associate Professor of Public Policy and Public Administration at George Washington University's Trachtenberg School of Public Policy and Public Administration and a Co-Director of the GW Regulatory Studies Center.

Executive Summary:

- In October 2023, the Food and Drug Administration's ("FDA") Office of Economics and Analysis ("OEA") released a preliminary Regulatory Impact Analysis ("RIA") to accompany FDA's proposed rule, "Medical Devices; Laboratory Developed Tests" ("Proposed Rule") as required by Executive Orders 12866 and 14094 for all rules deemed by the Office of Information and Regulatory Affairs ("OIRA") to be 3(f)1 significant.[2]

- OEA's RIA fails, on several dimensions, to adhere to the standards described in the academic literature as well as the Office of Management and Budget's ("OMB") Circular A-4, which provides guidance to agencies in producing RIAs that fulfill the requirements of the executive orders.[3] These issues result in an RIA that: 1) significantly understates costs by failing to quantify a key ancillary effect; 2) substantially inflates benefits by misusing benefit transfer methods; 3) provides limited ability to evaluate reasonable alternative regulatory approaches; and 4) offers minimal discussion of the distributional effects, including those on marginalized and underserved communities.

- In OEA's analysis, the primary benefits originate in the Proposed Rule's perceived role in reducing misdiagnoses from what OEA refers to as "problematic" laboratory developed tests ("LDTs"), which account for over 98 percent of the total benefits described in the RIA. Similarly concentrated, OEA's estimates of the costs are largely derived from one-time and ongoing reporting, registration, and approval process requirements for LDTs. Of these costs, close to 100 percent of one-time costs and roughly 89 percent of recurring compliance costs originate in premarket approval applications, 510(k) notifications, and De Novo requirements that would apply to LDTs.[4]

- The compliance costs OEA estimates that the Proposed Rule would impose on laboratories offering LDTs are substantial. Based on data provided in the RIA, laboratories would be required to use nearly three and a half years of their gross profits from LDTs just to be able to cover the one-time compliance costs introduced by the Proposed Rule. And this estimate does not account for the fact that gross profit excludes categories of costs that would substantially reduce what is available to laboratories to pay for these newly introduced compliance costs nor does it incorporate the actual fees

[2] Laboratory Developed Tests Proposed Rule Regulatory Impact Analysis, (Oct. 3, 2023), available at fda.gov/about-fda/economic-impact-analyses-fda-regulations/laboratory-developed-tests-regulatory-impact-analysis-proposed-rule. Subsequently, this RIA is referred to as "Proposed Rule RIA." Medical Devices; Laboratory Developed Tests Proposed Rule, 88 FR 68006 (Oct. 3, 2023); Executive Order 12866, Regulatory Planning and Review, 58 FR 51735 (Oct. 4, 1993); and Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023). All referenced material cited should be considered incorporated into this comment. I would be pleased to provide copies of any cited references (subject to copyright or paywall limitations).

[3] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003). OMB released an updated version of Circular A-4 on November 9, 2023. However, the previous version applies to RIAs for proposed, interim final, and direct final rules received by OIRA before March 1, 2024, and for final rules received before January 1, 2025. Therefore, OMB's 2003 version of the Circular applies to the Proposed Rule.

[4] Proposed Rule RIA, at pp. 53-4, 85.

laboratories would pay FDA to accompany submissions, which are considered transfers in the RIA.

- In addition to compliance costs, Circular A-4 explicitly requires agencies to consider ancillary costs in their RIAs.[5] Further, OEA acknowledges that the significant compliance costs they estimate have the potential to force laboratories to discontinue offering certain LDTs. However, they argue they are unable to estimate these ancillary costs due to lack of data. Still, using data already presented in the RIA coupled with the approach that OEA indicates it would employ to quantify this effect reveals that the Proposed Rule would put roughly 90 percent or more of existing LDTs at risk of no longer being offered. And this assumes that all existing LDTs requiring approval would be eligible for the most cost-effective pathway, which necessitates a predicate device so is not likely to be an option for many of them, something OEA acknowledges in their analysis.

- Utilizing the same monetary estimates OEA employs in the RIA to value the benefits of extending lives reveals that the associated annual costs from lost LDTs in shortening lives would likely be double OEA's estimate of the Proposed Rule's annual benefits. Moreover, these recurring health costs associated with at-risk LDTs leaving the market would easily surpass, in one year, any savings associated with a reduction in the already sizable one-time approval costs because at-risk LDTs would leave the market rather than be subjected to FDA's premarket approval process.

- Much like the RIA substantially understates the Proposed Rule's costs, it also significantly overstates its benefits. By extrapolating benefits from only one disputed study and misapplying the results of that study to develop an estimate of lives extended by substituting FDA-approved tests for so-called "problematic" LDTs, OEA fails to adhere to Circular A-4 principles for applying benefit transfer.[6] Even the study OEA cites indicates it is inappropriate to extrapolate to a broader set of LDTs from just their small-sample study. Further, utilizing more recent research that corrects for the errors of the flawed study on which OEA relies suggests the annual benefits are roughly one-third of what the RIA estimates.

- This does not even account for the fact that OEA's specific approach to measuring benefits assumes that all misdiagnoses from "problematic" LDTs will be eliminated by shifting to FDA-approved tests, an assumption OEA contradicts in the RIA and is not supported in the medical literature. Employing a simpler approach that avoids this issue and allows the analysis to incorporate a larger number of medical studies examining the relative level of accuracy of LDTs and FDA-approved tests, as Circular A-4 recommends, benefits are a quarter to one-half what the RIA estimates, consistent with results from correcting OEA's approach directly.

[5] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 26.
[6] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at pp. 24-6.

- Consideration of alternatives is especially important for the Proposed Rule because its considerable costs – both in complying with the rule and associated health effects from at-risk LDTs – coupled with much smaller benefits suggest that alternative, less draconian approaches may be preferred. It is notable that the current framework utilized by the Centers for Medicare & Medicaid Services ("CMS") under the Clinical Laboratory Improvement Amendments ("CLIA") to oversee laboratories that develop LDTs incorporates elements of an approach labeled management-based regulation in the academic literature, which is appropriately used in US regulatory contexts similar to the environment in which LDTs are developed and deployed, including by FDA itself.[7]

- In its analysis of alternatives, OEA also briefly describes but fails to quantify net benefits for two other regulatory approaches that would still phase out the general enforcement discretion approach for LDT registration, listing, and adverse event reporting but would not subject existing LDTs to premarket review requirements. The second would also continue general enforcement discretion for LDTs receiving approval from the New York State Clinical Laboratory Evaluation Program ("CLEP"), including those developed after the final rule.[8] Given the relevant market failure is asymmetric information, these options have the attractive quality that they feature information remedies, which Circular A-4 recommends in these types of cases.[9] Because many of the necessary elements are already available, presenting a quantitative analysis of the benefits and costs of these alternatives should not be overly burdensome for OEA. The primary source of uncertainty would be in estimating the proportion of new LDTs that would opt for approval under New York's CLEP rather than FDA's processes, which could be dealt with using relative cost data or reasonable assumptions.

- Finally, Circular A-4 directs agencies developing RIAs to analyze the distributional effects of the rule.[10] The impact of the Proposed Rule on LDT prices receives very limited attention in OEA's RIA. Yet, for LDTs that can remain in the market, providers will be forced to raise prices to manage the burden of significant additional compliance costs. As prices rise for health care services, including diagnostic tests, because of the Proposed Rule, quantity demanded will decrease, and more so for those with higher price elasticities, including low-income as well as underinsured and uninsured individuals. Given that the latter group especially is disproportionately concentrated among minorities, they will bear more of the burden in increased mortality rates as a result. Given the Biden administration's emphasis on broadening participation of traditionally underserved communities in the regulatory process, it would seem OEA must do much more to evaluate the distributional effects of the Proposed Rule than they currently do to fulfill adequately their obligations under Circular A-4.[11]

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[7] See, e.g., Coglianese, Cary, and David Lazer. "Management-Based Regulation: Prescribing Private Management to Achieve Public Goals." *Law and Society Review* (2003) 37(4): 691-730.
[8] Proposed Rule RIA, at pp. 100-3.
[9] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 9.
[10] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p 14.
[11] Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023).

- Resolving these issues – including quantifying ancillary costs, appropriately applying benefit transfer, quantifying the effects of meaningful alternatives, and considering the distributional effects of LDT price changes – will result in an RIA that adheres to basic principles outlined in Circular A-4 and reveals that, in fact, the quantified costs substantially exceed the quantified benefits of the Proposed Rule. Perhaps even more importantly, addressing these issues can allow OEA's RIA to fulfill its role in providing a transparent view of the likely effects of the Proposed Rule such that stakeholders and the public more generally can more accurately assess whether its benefits justify its costs.

I. Background

I was engaged by the American Clinical Laboratory Association ("ACLA") to assess OEA's preliminary RIA accompanying FDA's Medical Devices; Laboratory Developed Tests Proposed Rule.[12]

I am Associate Professor of Public Policy and Public Administration at George Washington University as well as a Co-Director of the GW Regulatory Studies Center. My expertise as an academic centers on regulatory policymaking, and my research has examined a variety of topics relevant for evaluating the application of economic analysis in specific regulatory contexts, including roles that analysis plays in agency regulatory decision-making, design of informative RIAs, factors that influence rule timing and durability, and the variety of approaches that regulatory agencies employ to achieve regulatory goals. In addition to publications in leading academic journals and edited volumes focused on regulation, public policy and administration, political science, and economics, I am the author of the Cambridge University Press book, *Structured to Fail? Regulatory Performance under Competing Mandates*, and a co-editor of the University of Pennsylvania Press volume, *Does Regulation Kill Jobs?* I hold a PhD in public policy from Harvard University, an MBA from the University of Chicago, and a BA in economics from Davidson College.

In conducting my examination, I reviewed the analysis prepared by OEA from the perspective of the procedures that FDA, or any executive branch regulatory agency, is to follow when developing an RIA to support a proposed rule. In performing this analysis, I was supported by staff of Global Economics Group, who worked under my direction.

My overarching conclusion is that the RIA does not fulfill the standards for economic analysis that federal agencies are to follow in several key areas. The discussion of the Proposed Rule's potential costs focuses primarily on compliance costs that laboratories will face in complying with the Proposed Rule if it is finalized while largely ignoring and failing to quantify, with available data, the ancillary and substantial negative health-related and mortality costs that will result from imposing a new regulatory framework on LDT providers. Additionally, the RIA makes inappropriate use of a benefit transfer approach to extrapolate benefits from only one disputed study and misapplies the results of that study to develop an estimate that significantly inflates the Proposed Rule's benefits.

These concerns, coupled with limited quantitative consideration of reasonable alternatives and key distributional effects, lead to an RIA that significantly overstates benefits, dramatically understates costs, provides limited ability to evaluate alternative approaches relative to the Proposed Rule, and obscures significant negative distributional effects on uninsured and traditionally underserved communities. Resolving these issues will result in an RIA that adheres to basic principles outlined in OMB guidance and reveals that, in fact, the quantified costs substantially exceed the benefits of the Proposed Rule. Perhaps even more importantly,

[12] Proposed Rule RIA. Medical Devices; Laboratory Developed Tests Proposed Rule, 88 FR 68006 (Oct. 3, 2023).

addressing these issues can allow OEA's RIA to fulfill its role in providing a transparent assessment of the likely effects of FDA's Proposed Rule such that stakeholders and the public more generally can more accurately assess whether its benefits justify its costs.

A. Analysis Requirements for Economically Significant Rules

OMB's Circular A-4 provides a set of principles to guide executive branch agencies in their preparation of RIAs, which are required by Executive Orders 12866 and 14094 for all rules deemed by OIRA to be 3(f)1 significant in order to demonstrate that the benefits of that rule justify its costs.[13] OIRA determined that FDA's Proposed Rule is 3(f)1 significant.[14]

These principles, as well as best practices established in the academic literature, offer clear guidance on the elements to be included in an RIA that fulfills the requirements of the executive orders.[15] These elements include:

1) a discussion of the need for the rule, based on the problem the rule seeks to remedy;
2) consideration of not just of the rule's direct benefits and costs but also the ancillary benefits and indirect costs or countervailing risks;
3) careful consideration of how studies are selected if benefit transfer methods are used, recognizing that other approaches to valuing benefits are generally preferred;
4) consideration of reasonable alternatives to the approach advocated by the agency; and
5) examination of the distributional effects of the rule in a separate analysis.

B. Discussion of the Central Components of OEA's RIA

The primary source of benefits in OEA's preliminary RIA derives from the Proposed Rule's role in reducing misdiagnoses from what they refer to as "problematic IVDs offered as LDTs."[16] OEA suggests that these annual benefits, which they estimate total $26.4 billion or $39.6 billion (depending on the choice of discount rate), will result from improved health outcomes in the form of reduced baseline mortality risk.[17] These benefits originate from an expected reduction in misdiagnoses from in-vitro diagnostic products ("IVDs") offered as LDTs and represent over 98 percent of the total benefits presented in the RIA.[18]

OEA's estimates of the costs of the Proposed Rule are similarly concentrated, with the majority derived from focusing on the compliance costs that would be imposed on laboratories associated with one-time and ongoing reporting, registration, and approval process requirements.

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[13] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003); Executive Order 12866, Regulatory Planning and Review, 58 FR 51735 (Oct. 4, 1993); and Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023).
[14] Medical Devices; Laboratory Developed Tests Proposed Rule, 88 FR 68027 (Oct. 3, 2023).
[15] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003); Executive Order 12866, Regulatory Planning and Review, 58 FR 51735 (Oct. 4, 1993); Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023); and see, e.g., Dudley, Susan, et al. "Consumer's Guide to Regulatory Impact Analysis: Ten Tips for Being an Informed Policymaker." *Society for Benefit-Cost Analysis* (2017) 8(2): 187-204.
[16] Proposed Rule RIA, at p. 1.
[17] Proposed Rule RIA, at pp. 53-4.
[18] Proposed Rule RIA, at p. 54.

Close to 100 percent of the $35.5 billion primary estimate of one-time costs and 89 percent of the $4.2 billion primary estimate of recurring compliance costs derive from the premarket review, 510(k), and De Novo requirements that would apply to LDTs within four years from FDA's publication of the final phaseout policy.[19]

II. The RIA's Estimate of the Proposed Rule's Costs

To put the Proposed Rule's one-time compliance costs in perspective, OEA's primary estimate of $35.5 billion is over 1.2 times their primary estimate of 2023 annual LDT revenues, which amount to $28.6 billion.[20] On average, publicly traded firms offering LDTs spend 64 percent of their revenue providing their services; the remaining 36 percent of revenue is the gross margin of the services before operating costs, such as overhead, salaries, research and development, and administrative expenses.[21] If one were to apply a gross margin of 36 percent (which significantly overstates the net economic margin from LDTs available to pay compliance costs) to OEA's primary estimate of 2023 annual LDT revenues, laboratories would be required to use nearly three and a half years of those gross margin profits on LDTs just to be able to cover the one-time compliance costs introduced by the Proposed Rule. And, as suggested, this does not even account for the fact that gross margin profits substantially overstate the actual cash after expenses that would be available to laboratories to pay for these newly introduced compliance costs. Moreover, these figures do not include the actual fees laboratories would need to pay to FDA to accompany their submissions for existing LDTs, which OEA estimates would total over $1.5 billion but are considered transfers since they represent revenue for FDA.[22] Perhaps most importantly, these costs represent just a fraction of the Proposed Rule's total potential costs.

A. Examining LDTs at Risk of Exiting the Market

In addition to compliance costs, explicitly considering countervailing risks or indirect costs is required by Circular A-4 and critical to gain a more complete understanding of the likely effects of the Proposed Rule.[23] This is especially true if the RIA is to allow stakeholders and the broader public to assess whether the benefits of the proposed rule justify its costs as Executive Order 12866 mandates.[24] OEA acknowledges the possibility that laboratories "may choose to exit the market or discontinue certain IVDs offered as LDTs due to compliance costs."[25] In

[19] Proposed Rule RIA, at p. 85.
[20] Proposed Rule RIA, at p. 27.
[21] Revenue and gross margin data were collected from publicly available information from Capital IQ for nine publicly traded laboratories that offer LDTs. The average gross margin weighted by revenue for these firms in 2022 was 36.2 percent, but gross margin does not take into account overhead, salaries, research and development, and administrative expenses. Moreover, this percentage represents an approximation, given that it considers a broader set of products and services than just LDTs. Measures of profits that account for operating expenses and opportunity costs are better measures to determine at-risk products or services. Despite the limitations of using gross margin, it is used throughout this analysis to be consistent with OEA's analysis of at-risk products in its Medication Guides: Patient Medication Information proposed rule.
[22] Proposed Rule RIA, at p. 94.
[23] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 26.
[24] Executive Order 12866, Regulatory Planning and Review, 58 FR 51735 (Oct. 4, 1993).
[25] Proposed Rule RIA, at p. 87.

addition, OEA suggests in the RIA an approach for estimating these costs by employing a similar methodology to what they utilized in their analysis of a previously published proposed rule, Medication Guides: Patient Medication Information.[26] Still, OEA indicates they are unable to estimate these indirect costs due to lack of data.

However, the information that is already presented in the RIA allows one to develop a sense of the magnitude of these costs. OEA's primary estimates for 2023 annual industry revenue and the number of LDTs on the market are $28.6 billion and 80,400 LDTs, respectively, suggesting that the average LDT generated $356,000 in annual revenue in 2023.[27] Even before considering the costs associated with performing these tests, it is instructive that the average LDT's annual revenue falls well below OEA's primary estimate of $4.38 million for a premarket application ("PMA") for approval as well as $565,000 for a De Novo classification request.[28] OEA estimates that FDA approval for a 510(k) submission ranges from $275,000 to $526,000 depending on the complexity of the study.[29] Therefore, many LDTs will have less annual revenue than the one-time cost for initial approval, and these costs ignore the actual fees paid by the laboratory to FDA, which is considered a transfer for purposes of OEA's analysis.

The large one-time costs for approval relative to the revenues for LDTs means that much of the industry is at risk of exiting the market. In their RIA assessing the economic effects of FDA's Medication Guides: Patient Medication Information proposed rule – which OEA indicated would inform their analysis for at-risk LDTs under the Proposed Rule[30] – OEA specified that the threshold for a product to be at risk is one that does not have enough sales "to cover the cost of [Patient Medication Information] without resulting in negative accounting profit."[31] OEA states, "For any product with positive annual sales less than its corresponding threshold…we determine that product to be at risk of exiting the market if it is not granted a waiver or extension of the requirements of [Patient Medication Information]."[32]

Applying OEA's threshold for at-risk products to the case of LDTs means tens of thousands of tests would be at risk even before considering that accounting profits are a fraction of the revenue they generate. Still, following OEA's proposed approach to focus on using gross margin to identify at-risk LDTs reveals even more clearly how much of the market would be at risk from the Proposed Rule. Assuming a gross margin of 36 percent, which, as described, represents a significant overestimate of the net economic margin from LDTs available to pay

[26] Proposed Rule RIA, at p. 88. OEA directs the reader to section II.G.1 "Count of At-Risk Products" in the Preliminary Regulatory Impact Analysis of the proposed rule Medication Guides: Patient Medication Information ("Medication Guide RIA"), (May 31, 2023) available at fda.gov/about-fda/economic-impact-analyses-fda-regulations/medication-guides-patient-medication-information-proposed-rule-preliminary-regulatory-impact.
[27] Proposed Rule RIA, at pp. 24-7.
[28] Proposed Rule RIA, at pp. 78, 81-4.
[29] Proposed Rule RIA, at pp. 81-3.
[30] Proposed Rule RIA, at p. 88.
[31] Medication Guide RIA, at p. 45.
[32] Medication Guide RIA, at p. 46.

compliance costs, the yearly gross profit for the average LDT is $128,160, still well below the cost of any approval process required by FDA.

Even considering the assumed sales growth rate used by OEA in the RIA, which would mean that the average LDT would generate $164,469 in gross margin by 2028, when all existing LDTs would be subjected to premarket review requirements, significantly more than 50 percent of tests would be at risk of no longer being offered employing OEA's established criterion. Stated differently, the gross profit of the average LDT would be less than 60 percent of the estimated cost of even the most cost-effective pathway to approval, the 510(k) with method comparison study, which requires a predicate device so is not likely to be an option for many LDTs. Moreover, this simple calculation does not even incorporate the fee that laboratories are required to pay as well as the reality that just as revenue may grow, so will the costs associated with preparing for the approval process.

Appealing to OEA's Tables A.2 and A.3 in Appendix A which contain estimates of LDT revenue and volume by firm size to support OEA's required analysis under the Regulatory Flexibility Act, one finds that the average LDT does not generate enough gross profit to avoid being at risk by OEA's definition for any category of firm size.[33] Assuming the same gross margin rate as before, average gross profit is $57,445 for LDTs from laboratories up to $100 million in annual revenue, and $259,541 for LDTs from laboratories over that size.

Those same data allow one to estimate the actual percentage of LDTs that may be at risk. Applying the assumed sales growth rate used by OEA in the RIA for LDT revenue and computing average gross profit across all size categories in 2028 when LDTs would be subject to the review requirements under the Proposed Rule, one can compute the estimated standard deviation of the distribution. Doing so and assuming LDT gross profits follow a normal distribution suggests that just over 90 percent of the universe of existing LDTs might be at risk because their gross profit is below the estimated cost of the 510(k) with method comparison study approach, even if costs are assumed to grow at only half the rate of revenues and OEA's estimate of the associated submission fee is weighted by firm size. And the associated percentage of LDTs at risk climbs to close to 95 percent if one simply applies OEA's 2023 data directly to perform the calculations, comparing the estimated 510(k) with method comparison cost including a weighted average of the associated submission fee against OEA's described distribution of laboratory LDT revenue.

Further, even these estimates understate the number of LDTs at risk since they rely on gross profit rather than operating profit or, even more accurately, economic profit. Gross margin does not incorporate the full set of costs facing a firm, such as overhead, research and development, and opportunity cost, that economic profit or even operating profit would consider. As OEA even notes in its RIA assessing the economic effects of FDA's Medication Guides: Patient Medication Information proposed rule, using gross profit "in the calculations results in

[33] Proposed Rule RIA, at pp. 124-6.

threshold [revenue] values that are smaller than if we were to use economic profit. Because of this, our estimates of at-risk products may represent lower bounds."[34]

B. Comparing Social Costs of At-Risk LDTs to the Proposed Rule's Benefits

In its computation of compliance costs, OEA assumes, without explanation, that only 50 percent of LDTs would require a premarket submission, with the other 50 percent exempt from the requirements. In fact, in the two places in the RIA where this assumption is stated, the other section is referenced, with no support provided in either place.[35]

Nevertheless, assuming this assumption is accurate, it would mean that 40,200 of the estimated 80,400 LDTs would require a premarket submission. To gain a sense of the magnitude of the health costs connected to the loss of roughly 90 percent of the existing stock of LDTs subject to approval under the Proposed Rule, one can apply OEA's estimates of the social value per case of an accurate diagnosis, which they use to value the benefits of the Proposed Rule. Much like FDA asserts in its analysis of the benefits of shifting from LDTs to FDA-approved tests in extending patient lives, an extensive medical literature highlights the critical role that LDTs play in delivering accurate diagnoses to save patients with potentially life-threatening conditions.[36] Thus, not having those potentially life-saving tests at all, or forcing medical personnel to shift to tests less appropriate for detecting the underlying condition accurately, can result in premature mortality in much the same way that having a more accurate test can extend a patient's life, as OEA suggests.

Applying OEA's computation for the social value per case of an accurate diagnosis, and assuming that each lost LDT results in just one additional life that is not extended on average because the test is no longer available that year, the annual health cost in 2022 dollars would be

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[34] Medication Guide RIA, at p. 46.

[35] Proposed Rule RIA, at pp. 68, 75. In section II.F.2, OEA notes, "As described in section II.F.4, we estimate that 50% of IVDs require a premarket submission." In section II.F.4, OEA notes, "As mentioned in section II.F.2, we estimate that approximately 50% of IVDs currently undergo premarket review."

[36] See, e.g., Caliendo, Angela M., et al. "Maintaining Life-saving Testing for Patients with Infectious Diseases: Infectious Diseases Society of America, American Society for Microbiology, and Pan American Society for Clinical Virology Recommendations on the Regulation of Laboratory-developed Tests." *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* (2016) 63(2): 151-4; Dimmock, David, et al. "Project Baby Bear: Rapid Precision Care Incorporating rWGS in 5 California Children's Hospitals Demonstrates Improved Clinical Outcomes and Reduced Costs of Care." *The American Journal of Human Genetics* (2021) 108(7): 1231-8; Marzinke, Mark A., et al. "The VALIDity of Laboratory Developed Tests: Leave It to the Experts?" *Journal of Mass Spectrometry and Advances in the Clinical Lab* (2023) 27: 1-6; Ricker, Charité, et al. "Increased Yield of Actionable Mutations Using Multi-gene Panels to Assess Hereditary Cancer Susceptibility in an Ethnically Diverse Clinical Cohort." *Cancer Genetics* (2016) 209(4): 130-7; Rummel, Seth K., et al. "Should Genetic Testing for Cancer Predisposition Be Standard-of-Care for Women with Invasive Breast Cancer? The Murtha Cancer Center Experience." *Cancers* (2020) 12(1): 234; Sun Li, et al. "A Cost-effectiveness Analysis of Multigene Testing for All Patients with Breast Cancer." *JAMA Oncology* (2019) 5(12): 1718-30. The majority of genetic tests, as discussed in the referenced literature, are understood to be LDTs. *See,* (*"*The majority of genetic tests – a type of IVD that analyzes various aspects of an individual's genetic material (e.g., DNA, RNA) – are LDTs.") Sarata, Amanda K. *"*FDA Regulation of Laboratory-Developed Tests (LDTs)." *Congressional Research Service.* (December 7, 2022).

between $52.8 and $79.6 billion using OEA's central estimates. These calculations follow from multiplying the number of LDTs that would be at risk of exit based on OEA's stated threshold by the per case value of an accurate diagnosis, as described by OEA.[37] The variation in the computation results from whether the estimates of the value of a statistical life year are computed using either a three or seven percent discount rate. Further, these costs assume that OEA's estimates of how lives are extended through an accurate diagnosis – which they derive by focusing on cancer specifically – are applicable to a broader range of conditions for which LDTs are used.[38] Of course, this is precisely what OEA assumes in their analysis of the benefits of the Proposed Rule as well.[39]

The bottom line is that, under these relatively conservative assumptions, the annual health costs associated with at-risk LDTs leaving the market would easily surpass any savings associated with a reduction in one-time approval costs because those at-risk LDTs would not be subjected to premarket approval, given they were no longer being offered at all. Stated differently, if the proposed rule's one-time costs associated with premarket approval requirements were even reduced by 90 percent, equivalent to $32 billion, due to LDTs exiting the market, the resulting reduction would still be substantially less than the estimated societal costs from lives shortened in one year of $52.8 to $79.6 billion because of the Proposed Rule. And, unlike the one-time compliance costs, the costs associated with premature mortality from lost LDTs are recurring welfare costs, meaning these costs are incurred every year.

In the end, there is simply not enough LDT revenue dollars to move a significant portion of LDTs through the approval process. Given what OEA has proposed as the distribution of LDTs that would need PMA, 510(k), and De Novo approvals – the one-time submission costs and fees to get existing LDTs through approval would total $33.5 billion.[40] With only $28.6 billion in annual revenue and $10.3 billion in gross margin, at most there would only be enough revenue to move 2,238 of OEA's estimate of 4,020 LDTs through the PMA approval process before every single dollar of revenue would be exhausted – leaving 94 percent (or 37,962) of LDTs without any funds to attempt approval.[41] And this assumes that the 50 percent of LDTs, or

[37] Proposed Rule RIA, at pp. 33-7.
[38] Proposed Rule RIA, at pp. 33-40.
[39] Embedded in the assumption that each lost LDT is associated with just one additional life not extended is the reality that some LDTs extend many lives per year, and others may extend close to zero, either because there are comparable alternatives for the LDT, or the underlying condition will not shorten the individual's life. Also incorporated in this assumption is the recognition that all tests are imperfect, such that a small subset of lives shortened might not have been extended because of a test error (e.g., a false negative) had the test been performed.
[40] OEA estimates 4,020 of existing LDTs will go through PMA applications with $4.38 million in submission costs and $.23 million in fees to FDA; 4,020 LDTs will go through with De Novo classifications with $.56 million in submission costs and $.70 million in fees; 18,974 LDTs will go through 510(k) method comparison studies with $.27 million in submission costs and $.10 million in fees; and 13,186 LDTs will go through 510(k) moderately complex clinical studies with $.53 million in submission costs and $.10 million in fees. See Tables 25, 28, 29, 30 and 34 of the Proposed Rule RIA.
[41] Assuming the same gross margin rate as before, each PMA approval would need $12.79 in annual revenue to have enough proceeds to handle $4.38 million in submission costs and $.23 million in fees (($4.38 million + $.23 million)/.36 = $12.79 million). With total annual industry revenues of $28.6 billion, at most 2,238 LDTs could go through PMA before all remaining LDTs would be at risk ($28.6 billion/$12.79 million = 2,238).

40,200, that OEA claims would not need to go through the FDA approval process collectively do not earn a single dollar of revenue, obviously an illogical assumption.

Using the described cost estimation approach derived from data already presented in OEA's RIA, it becomes clear that at least one source of cost that OEA only discusses qualitatively actually exceeds the costs that are estimated. These costs associated with lost LDTs also exceed OEA's comparable estimate of the Proposed Rule's annual benefits, which amount to $26.8 billion with a three percent discount rate and $40.0 billion under a seven percent discount rate. Adding in the one-time benefits that OEA computes, which range from $4.1 billion to $6.8 billion using a three or seven percent discount rate respectively, the annual cost derived solely from lost LDTs would substantially exceed the benefits in any given year.

Further, the computation of the costs of lost LDTs presented here, whose size already exceeds the estimated benefits of the Proposed Rule, does not even consider the related costs of lost innovation for those LDTs that remain in the market. It is quite common for an LDT to be modified during the course of its use to improve the quality of the test and adapt to changing conditions. A 2018 study published in *JAMA Oncology* reported that more than 60 percent of the laboratory participants in their study of the relative performance of FDA-approved and lab developed oncology tests reported modifying their FDA-approved test "to broaden clinical practice, rendering them LDTs."[42] Under the Proposed Rule, these improvements would, in most cases, require FDA approval, thus significantly reducing the number of modifications that could be made given the financial costs and time connected to doing so.

C. Using Industry Evidence to Substantiate Estimated Costs from Lost LDTs

The described estimates associated with the potential for lost LDTs are consistent with data from laboratories competing in the LDT market. Responses from an informal survey of representative members of the ACLA revealed that the overwhelming majority of LDTs they offer gross less than $5 million in revenue per year. Using the previously described estimated gross margin percentage, annual gross profit for these tests thus amounts to several times less than OEA's estimate of the cost of taking any of these tests through the premarket approval process. In reality, annual revenue from most LDTs is much less than even this simple estimate might suggest. For example, one laboratory company reported that over 40 percent of the substantial set of LDTs that the company offers generate revenue less than even the fiscal year 2024 510(k) user fee of $21,760.

These data from industry participants reveal that the previously discussed calculations using OEA's data – which suggest both that a large majority of LDTs offered in the market would be at risk and that the associated welfare costs under FDA's proposed approach to oversight would be substantial – are decidedly reasonable. These at-risk assays would range from LDTs important in determining the care for patients with hematologic disease to those distinguishing rare forms of anemia from other blood conditions; and from tests used for the

[42] Kim, Annette S., et al. "Comparison of Laboratory-Developed Tests and FDA-Approved Assays for *BRAF*, *EGFR*, and *KRAS* Testing." *JAMA Oncology* (2018) 4(6): 838-841.

diagnosis of rare inherited metabolic diseases to tests available to help diagnose Rhett Syndrome, a rare neurological disorder that causes the loss of motor and language skills most commonly in girls.

In sum, by solely focusing on compliance costs in the RIA, OEA has failed to monetize a critical category of costs that has the potential for health effects resulting from LDTs exiting the market that substantially exceed the supposed benefits of the Proposed Rule. This represents a failure of the RIA to meet the standards outlined in Circular A-4 for economic analysis in rulemaking.[43] Conducting an RIA requires consideration of the direct and indirect effects of that regulation, including any potential unintended consequences of the proposal; moreover, an RIA must treat benefits and costs in a symmetric way in performing the analysis. Thus, it is not sufficient to simply consider possible health benefits associated with eliminating or reducing the number of, in FDA's words, potentially "problematic" LDTs without simultaneously considering the costs connected to the potential loss of welfare-enhancing and lifesaving LDTs that might no longer be offered. These costs arise because of the significant financial costs associated with complying with the regulatory framework relative to the revenue generated by laboratories in producing and performing LDTs.

III. The RIA's Estimate of the Proposed Rule's Benefits

Much like with the computation of costs, OEA's assessment of the benefits of the Proposed Rule also presents several issues. As described, over 98 percent of the total quantified benefits result from the Proposed Rule's suggested ability to reduce misdiagnoses from "problematic" LDTs. OEA estimates a baseline annual total of 19,000 fatal cases that receive a misdiagnosis due to "problematic" LDTs, all of which they claim would be prevented by the Proposed Rule. To reach that estimate, OEA starts with a primary estimate of 160,000 misdiagnosis fatalities associated with conditions other than heart disease. This figure is then reduced by 50.0 percent to account for testing that occurs outside of IVDs and then another 50.0 percent to account for testing done by IVDs that are not LDTs. Finally, of the remaining misdiagnoses attributable to LDTs, OEA assigns 47.4 percent as their estimate of the probability the misdiagnosis resulted from an LDT that is "problematic," yielding 19,000 misdiagnoses from "problematic" LDTs.[44] They determine that each misdiagnosis avoided has a benefit value of $1.46 million at a three percent discount rate and $2.2 million at a seven percent discount rate – resulting in aggregate annual benefits of $26.3 billion and $39.5 billion depending on the discount rate used.[45]

Among other issues in their computation of benefits, OEA does not adhere to established principles for preparing RIAs in two critical areas, which results in estimates of the health benefits of the Proposed Rule that are substantially inflated. First, the RIA makes inappropriate use of a benefit transfer approach to extrapolate benefits by using a single disputed study of LDT analytical accuracy, relative to including references to additional research that suggest the

[43] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 26.
[44] Proposed Rule RIA, at p. 39.
[45] Proposed Rule RIA, at pp. 37-40.

probability employed by OEA to measure the likelihood that an LDT is "problematic" is far too high. This is true both because the study they rely on is flawed and because the literature, more generally, reaches different conclusions. Second, OEA incorrectly assumes that every fatality resulting from a misdiagnosis due to a "problematic" LDT will be eliminated under the Proposed Rule – an assumption that is unsupportable and contradicted by the studies OEA relies on elsewhere in the RIA. As OEA itself asserts, "no test is perfect 100% of the time,"[46] and diagnosis is determined by leveraging clinical inputs beyond test results.

A. Evaluating the Appropriateness of OEA's Benefit Transfer Approach

One approach to valuing benefits in an RIA is to employ what is known as benefit transfer. Benefit transfer uses existing estimates of benefits from other studies and applies them to a new context, which in rulemaking means the context in which the rule is being contemplated. As described in Circular A-4, this method should "be treated as a last-resort option and not used without explicit justification" for a variety of reasons, including that the findings of the studies may pertain to a particular setting that is not reflective of the circumstances associated with the rulemaking.[47]

In evaluating studies to include, Circular A-4 advises that "selected studies should be based on adequate data, sound and defensible empirical methods and techniques." Moreover, populations represented in the research and the regulatory context should be similar, and the "market size (e.g., target population) between the study site and the policy site should be similar." For example, the Circular notes that "a study valuing water quality improvement in Rhode Island should not be used to value policy that will affect water quality throughout the United States."[48]

In the Proposed Rule, the assumption that is in large part responsible for the quantified benefits is OEA's estimate that 47.4 percent of LDTs are "problematic."[49] To arrive at that figure, OEA relies on a 2022 study published by Pfeifer et al. in the *American Journal of Clinical Pathology*, in which the authors examined performance for 19 laboratories employing LDTs to determine whether a patient was well-suited for a specific type of therapy for metastatic colorectal cancer.[50] The authors found that 9 of the 19 labs, or 47.4 percent, had five or more errors, which were predominately false negatives and which reflected an error rate greater than the statistical inaccuracy of a companion FDA-approved test. OEA then uses a benefit transfer approach to extrapolate from that result to assert that 47.4 percent of all LDTs are "problematic" and, thus, a significant number of lives associated with preventable misdiagnosis could be extended under the Proposed Rule.[51]

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[46] Proposed Rule RIA, at p. 37.
[47] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 24.
[48] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 25.
[49] Proposed Rule RIA, at p. 38.
[50] Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-38.
[51] Proposed Rule RIA, at p. 38.

OEA's approach raises significant issues. It is inappropriate to use a single, small study focused on one disease to characterize the performance of all LDTs across all testing disciplines. Pfeifer et al. (2022) explicitly recognize in their research the issues in making a generalized extrapolation to a large population of laboratories from their work in suggesting, "our study consisted of a relatively small number of nonrandomly selected laboratories….These laboratories and their respective LDTs may not represent the broader landscape of laboratories that perform clinical NGS in CLIA-certified environments."[52]

Perhaps even more importantly, the Pfeifer et al. (2022) study is already outdated. A more recent 2023 analysis of the same SPOT/Dx pilot data by Zehir et al. (2023) concludes that the SPOT/Dx pilot had multiple design and analytic differences with established proficiency testing programs. After remedying those issues, the authors reach a fundamentally different conclusion, explaining that LDTs exhibit "excellent" analytical performance.[53] Zehir et al. (2023) explain that most of the false negatives reported by laboratories in the SPOT/Dx pilot were the result of variants being tested with mean variant allele fractions ("VAFs") below the participant laboratories' limit of detection ("LOD"). As the authors' note, under the CLIA standards, laboratories are only expected to detect and report variants with criterion standard VAFs at or above their laboratory's assay LOD. Once laboratories are evaluated against the test results they can be expected to detect and report, more than half of what OEA determines to be "problematic" LDTs are no longer "problematic." In fact, Table 3 of Zehir et al. (2023) indicates that only four of 19 LDTs reported five or more false negatives, not nine of 19 as reported by Pfeifer et al. (2022).[54]

Because OEA heavily relies on Pfeifer et al. (2022) in their estimates of benefits, this seemingly small change in the analysis of the SPOT/Dx pilot data has a large impact on the aggregate benefits of the Proposed Rule. Shifting from nine "problematic" LDTs to four of 19 LDTs – meaning 47.4 percent to 21.1 percent – cuts out over half of the expected health benefits

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[52] Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-38, at p. 636.

[53] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at pp. 6-7. "Our analysis of the SPOT/Dx pilot results using methods modeled after established PT programs shows that, contrary to the reported conclusions of the original SPOT/Dx pilot, laboratory performance for KRAS and NRAS SNVs was excellent, both in wet and dry engineered samples. The overall detection rate for SNVs was 96.8%. The reanalysis confirmed that MNVs, although exceptionally rare or never observed in colorectal cancer, were detected at lower rates than SNVs, with an overall detection rate of 81.1%."

[54] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine.* (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at Table 3. Eliminating some of the tests from the analysis to account for tests that were below the participant's LOD could move the statistical z-score threshold of five or more test down to a lower number (e.g., four or more). Reevaluating the statistical threshold to account for this, none of the results change. All labs with four of less false negatives are not statistical different from the FDA-approved diagnostic.

of the Proposed Rule. With this correction, the aggregate benefits range from $11.7 to $17.6 billion, not $26.3 to $39.5 billion as reported in the RIA.

However, this is not the only problem that results from OEA's reliance on Pfeifer et al. (2022). Zehir et al. (2023) also note that a little over half of the false negative test results in the SPOT/Dx pilot were related to multinucleotide variants ("MNVs") that are extremely rare or never observed in reality. As Zehir et al. (2023) describe, "[a]nother important difference between the SPOT/Dx pilot and PT programs was the inclusion of a disproportionately high number of MNVs. KRAS or NRAS MNVs are so rare that there are no examples in the AACR GENIE dataset (public release v12) of 14,328 colorectal carcinomas, yet they comprised nearly a quarter (12/54; 22.2%) of the variants in the pilot."[55]

By extrapolating from Pfeifer et al. (2022), OEA is disproportionately relying on false negatives from extremely rare or never observed MNVs in colorectal cancer to then determine what portion of the general population of tens of thousands of LDTs are "problematic." This application of benefit transfer fails to adhere to the Circular A-4 principles on several dimensions, including choosing studies "based on adequate data, sound and defensible empirical methods and techniques," those in which the "study context and policy context…have similar populations," and those where the associated "good, and the magnitude of the change in that good [are] similar in the study and policy contexts."[56] As Zehir et al. (2023) notes, the type of generalizing employed in the RIA is even a problem in evaluating oncology testing, let alone all LDTs:

> *Results obtained from a small pilot study focused on one disease with rare or never-reported variants at low VAFs cannot be generalized to overall laboratory performance for all types of cancer. The pilot results only reflect laboratory performance for the study samples, which represent a minute percentage of samples encountered in routine clinical practice. As stated by Harada and Mackinnon, although the MNVs in the pilot "...serve the purpose of challenging a laboratory's informatics pipeline, they do not simulate a real-world situation," and the study design "...does not fully align with pan-tumor genomic analysis, which most laboratories are currently implementing."...The conclusions of the SPOT/Dx pilot about variable accuracy in the detection of genetic variants among some LDTs only apply to the samples with uncommon mutations at low-level VAFs included in the pilot and not to the performance of NGS LDTs overall.*[57]

Of the four remaining laboratories with alleged analytical accuracies significantly lower than the FDA-approved companion diagnostic, one of them had all of their false negatives derive

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[55] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine.* (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at p. 8.
[56] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 25.
[57] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine.* (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at p. 9.

from the extremely rare or never observed MNVs that Zehir et al. (2023) and others conclude cannot be applied to real-world situations.[58] With this correction, only three remaining LDTs out of 19 demonstrate an analytical difference with the FDA-approved companion diagnostic. As a result, the benefits from OEA's extrapolation fall to a range of $8.8 billion to $13.2 billion, meaning that annual benefits are actually one-third of what was estimated by OEA.

B. Assessing the Benefits Associated with Shifting to FDA-Approved Tests

In addition to more accurately characterizing the extent to which "problematic" LDTs exist, OEA must also consider the analytical accuracy of FDA-approved tests relative to the baseline of no change in the regulatory framework to be able to adequately measure the benefits of the Proposed Rule. As described, OEA readily admits that no test is perfect, indicating "an IVD that yields a false result in an individual case is not necessarily a problematic IVD (indeed, no test is perfect 100% of the time)."[59] As a result, benefits from improved testing outcomes should be measured based on the incremental improvements in accuracy rates.

However, rather than evaluating incremental improvements, OEA's approach to measuring benefits assumes that all misdiagnoses from "problematic" LDTs will go away under the proposed regulatory regime. Still, the RIA provides no basis for this assumption nor is it at all supported in the medical literature. Moreover, the approach OEA employs, using the probability of being a "problematic" LDT in its benefit calculation, is unnecessary and simply adds a complicated assumption to try to estimate.

OEA could have avoided this step altogether simply by comparing the analytical accuracy of LDTs generally to FDA-approved diagnostics and used that as the basis for determining how many misdiagnoses could be avoided. For example, if LDTs have an analytical accuracy of 97 percent compared to 98 percent for FDA-approved diagnostics, then it would be reasonable to expect that roughly one-third of the misdiagnoses could be avoided (by moving from a three percent error rate to a two percent error rate).[60]

Academic studies, including those referenced in the RIA, find that the analytical accuracy differences between LDTs and FDA-approved diagnostics are actually not far apart and, as a result, suggest that benefits of the Proposed Rule are far lower than what OEA proposes. For example, in their study that appeared in *JAMA Oncology*, Kim et al. (2018) find a high rate of accuracy and comparable performance of LDTs and FDA-approved diagnostics for three

[58] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at p. 8. Laboratory 13 had eight false positives reported in Pfeifer et al. (2022), all of which were related to MNVs.
[59] Proposed Rule RIA, at p. 37.
[60] For example, assuming these assumptions about relative accuracy rates are correct, if there are 10,000 tests performed with LDTs, roughly 300 misdiagnoses would result. If, instead, those 10,000 tests were performed with FDA-approved diagnostics, roughly 200 misdiagnoses would result, suggesting a 33 percent reduction.

common oncology analytes: BRAF, EGFR, and KRAS. The overall accuracy for LDTs was 97.1 percent relative to 97.5 percent for FDA-approved diagnostics.[61]

Similarly, a 2019 study by Moncur et al. (2019) compares the performance of different assay methods on College of American Pathologists proficiency testing for variant analysis for BRAF, EGFR, and KRAS. Their findings demonstrate the high degree of accuracy and comparable performance across all laboratories, regardless of methodology. In fact, the authors report a percentage of acceptable proficiency testing for FDA-approved diagnostics of 97.5 percent and 97.2 percent for LDTs.[62]

Moreover, even Pfeifer et al. (2022) – the paper that OEA relies on for other aspects of its benefits calculation – notes that the FDA comparison is not analytically perfect, suggesting, "[t]he CDx has a published positive percent agreement of 98.7% and negative percent agreement of 97.6%."[63] Using the Zehir et al. (2023) reanalyzed data, the negative percent agreement rate of the LDT labs analyzed was 96.8 percent for single-nucleotide variants.[64]

Using estimates from these studies suggests the benefits of moving from LDTs to FDA-approved diagnostics could marginally improve analytical accuracy from 97.2 percent to 97.5 percent on the lower end – which would be expected to reduce misdiagnosis errors by 10.7 percent.[65] Or, on the high end, analytical accuracy could be improved from 96.8 percent to 97.6 percent using Pfeifer et al. (2022) and Zehir et al. (2023) – which corresponds with an expected reduction in misdiagnosis errors by 25 percent.[66] Applying these ranges to OEA's baseline annual estimate of misdiagnosis fatalities from LDTs suggests the resulting decreases in misdiagnoses correspond to only 22.6 percent or 52.8 percent of OEA's estimate, further indicating a substantial drop in benefits, which now range from $6.0 to $20.9 billion at the upper bound, corresponding to roughly a quarter to half of what OEA suggests.

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[61] Kim, Annette S., et al. "Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing." *JAMA Oncology* (2018) 4(6): 838-41.

[62] Moncur, Joel T., et al. "Performance Comparison of Different Analytic Methods in Proficiency Testing for Mutations in the BRAF, EGFR, and KRAS Genes: A Study of the College of American Pathologists Molecular Oncology Committee." *Archives of Pathology and Laboratory Medicine* (2019) 143(10): 1203-11.

[63] Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-638, at p. 633.

[64] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at pg. 4. The authors determined that under their reanalysis the number of false negatives associated with SNVs was 24 of 740 tests performed.

[65] Percent Reduction = (LDT Error Rate – FDA Error Rate)/LDT Error Rate; 10.7 percent = (2.8 percent - 2.5 percent)/2.8 percent.

[66] 25.0 percent = (3.2 percent - 2.4 percent)/3.2 percent. Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-38; Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp.

Importantly, in addition to being a more direct method and avoiding a need to unrealistically assume that FDA-approved tests have accuracy rates of 100 percent, the alternative approach described also considers a breadth of publications as the guidance in Circular A-4 suggests an agency applying benefit transfer should do, relative to using just one disputed study. Moreover, the estimates of lives extended are consistent with the described corrected analysis using a combination of Pfeifer et al. (2022) and Zehir et al. (2023).[67]

IV. Other Important Considerations in Preparing the RIA

In addition to computing benefits and costs of the Proposed Rule, agencies are required in preparing an RIA to assess reasonable alternative regulatory approaches. In doing so, the agency must evaluate the benefits and costs, both quantitatively and qualitatively, of the main alternatives identified by the analysis in addition to its proposed rule. Moreover, because benefit-cost analysis focuses on economic efficiency and can obscure how benefits and costs are allocated among different sub-populations, Circular A-4 further directs agencies to "provide a separate description of distributional effects…so that decision makers can properly consider them along with the effects on economic efficiency."[68] Distributional effects should be "described quantitatively to the extent possible" when they "are thought to be important."[69]

A. Considering Reasonable Alternatives to FDA's Preferred Approach

According to Circular A-4, alternatives that the agency "should consider" include contemplating different approaches to enforcement, varying the level of stringency, utilizing different regulatory instruments, particularly those that do not involve design standards and direct controls, and applying different standards for different types of regulated entities including those based on size or geography.[70] Consideration of alternatives is particularly important for FDA's Proposed Rule because, as described, its considerable costs, both in complying with the rule as well as the associated health effects from at-risk LDTs, raise questions around whether the benefits justify the costs.

In its assessment of alternatives in its RIA, OEA primarily focuses on variation in the timeline for compliance. In fact, these are the two alternatives for which the analysis provides quantitative estimates of both benefits and costs.[71] The first alternative shortens the phaseout period while the second alternative lengthens it. Because the regulatory approach otherwise remains the same, the computed changes in benefits and costs derive primarily from differences in when they are realized and the associated effects of discounting. As a result, the quantitative

[67] Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-38; Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp.
[68] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 14.
[69] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 14.
[70] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 7-9.
[71] Proposed Rule RIA, at p. 97-100.

estimates are qualitatively similar to those for the Proposed Rule. Any analysis implementing the previously discussed recommendations to reassess the benefits and account for health-related costs connected to lost LDTs would yield quantitative estimates similar to what is described in this letter. For these reasons, focusing on the timeline for compliance is not all that helpful as a pathway to suggest meaningful alternatives that foster transparency and public participation in the rulemaking process for the Proposed Rule.

A developed academic literature on regulatory politics and policy has examined the breadth of regulatory instruments agencies may consider that can improve upon the limitations of more traditional, direct controls, of which FDA's Proposed Rule is one example.[72] One of these approaches, management-based regulation or enforced self-regulation, requires regulated entities to develop plans to manage risks associated with their operations to flexibly achieve regulatory objectives.[73] After developing their plans, these same organizations are required to receive the associated regulator's approval. From the regulator's perspective, employing management-based regulation is most appropriate when the regulated community is characterized by a large number of heterogenous entities with regulated outputs that are difficult to observe and monitor. This is a set of circumstances that aptly characterizes the environment in which LDTs are developed and employed.

It is notable that the current framework utilized by CMS under CLIA to oversee laboratories, including those that develop LDTs, has elements of a management-based regulatory framework. Moreover, it is an approach that is actually employed by FDA itself in at least one other similar context, food safety regulation.[74] For example, CMS' regulatory approach focuses attention on the operations of the laboratory and qualifications and training of the associated staff. It imposes on laboratories the requirement that they develop and implement quality control procedures "to monitor the accuracy and precision of the complete testing process."[75] Through its Individualized Quality Control Plan (IQCP) program, laboratories also have the opportunity to tailor their quality control plans to the realities of their "unique testing environments and patients."[76]

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[72] See, e.g., Carrigan, Christopher, and Cary Coglianese. "The Politics of Regulation: From New Institutionalism to New Governance." *Annual Review of Political Science* (2011) 14: 107-129; Richards, Kenneth R. "Framing Environmental Policy Instrument Choice." *Duke Environmental Law & Policy Forum* (2000) 10(2): 221-286.

[73] Ayres, Ian, and John Braithwaite. *Responsive Regulation: Transcending the Deregulation Debate*. New York: Oxford University Press (1992); Bardach, Eugene, and Robert A. Kagan. *Going by the Book: The Problem of Regulatory Unreasonableness*. Philadelphia: Temple University Press (1982); Coglianese, Cary, and David Lazer. "Management-Based Regulation: Prescribing Private Management to Achieve Public Goals." *Law and Society Review* (2003) 37(4): 691-730.

[74] Coglianese, Cary, and David Lazer. "Management-Based Regulation: Prescribing Private Management to Achieve Public Goals." *Law and Society Review* (2003) 37(4): 691-730.

[75] CMS, CLIA Individualized Quality Control Plan: Considerations When Deciding to Develop an IQCP (Nov. 2014), available at cms.gov/regulations-and-guidance/legislation/clia/downloads/cliabrochure12.pdf, at p. 1; CMS, CLIA Individualized Quality Control Plan: What is an IQCP? (Nov. 2014), available at cms.gov/regulations-and-guidance/legislation/clia/downloads/cliabrochure12.pdf.

[76] CMS, CLIA Individualized Quality Control Plan: Considerations When Deciding to Develop an IQCP (Nov. 2014), available at cms.gov/regulations-and-guidance/legislation/clia/downloads/cliabrochure12.pdf, at p. 1.

In so doing, the current regulatory framework employed by CMS for LDTs shares similarities, both in its design as well as in the characteristics of the associated regulated laboratories, to other US contexts in which regulators are currently employing management-based regulation effectively. These include the aforementioned FDA and the US Department of Agriculture's Food Safety Inspection Service for food production and the Occupational Health and Safety Agency for industrial chemical manufacturing to promote safe operations in their respective policy domains.[77] Thus, CMS' current approach to regulating LDTs is certainly not without precedent in similar contexts. CMS' regulatory approach adds additional elements as well. For example, in the current regulatory environment, LDTs are also subjected to proficiency testing to ensure analytical validity and periodic CMS laboratory inspections that are characteristic of some, but not all, management-based regulatory environments.

Beyond considering variation in the compliance timeline, OEA also briefly describes but does not attempt to quantify net benefits for two other regulatory approaches that would still phase out the existing general enforcement discretion approach for LDTs with respect to certain regulatory requirements connected to the Proposed Rule, including registration, listing, and adverse event reporting.[78] Moreover, they would still mandate that new LDTs as well as existing LDTs that undergo changes receive FDA approval. However, they would not subject LDTs in existence at the time of the final rule to premarket review requirements. In addition, the second of these two regulatory alternatives would also continue general enforcement discretion for LDTs that receive approval from the New York State's CLEP, even LDTs developed after the final rule.[79]

One attractive element of these latter two alternatives is that they consider the economic market failure the Proposed Rule attempts to address and tailor the approach to more specifically remedy that issue. Although not identified by OEA, the market failure in this case is asymmetric information, which as described in Circular A-4, suggests "informational remedies will often be preferred," as they provide "consumers a greater choice than a mandatory product standard or ban,"[80] which is what FDA is instead proposing. For example, by exempting many LDTs from premarket review requirements while retaining labeling requirements under stage two, FDA can specifically address the failure using a relatively lower cost approach, as OEA's primary estimates of $2.75 million in one-time and $220,000 in recurring compliance costs associated with the labeling requirement suggest.[81]

Much like the Proposed Rule, quantifying the benefits and costs of these two alternatives exempting existing LDTs from premarket review would likely still yield negative net benefits, at least after accounting for the sizable indirect costs associated with at-risk LDTs and a more reasonable application of benefit transfer in assessing the implications of eliminating "problematic" LDTs. However, the magnitude of the imbalance between costs and benefits is

[77] Coglianese, Cary, and David Lazer. "Management-Based Regulation: Prescribing Private Management to Achieve Public Goals." *Law and Society Review* (2003) 37(4): 691-730.
[78] Proposed Rule RIA, at p. 100-3.
[79] Proposed Rule RIA, at p. 102-3.
[80] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 9.
[81] Proposed Rule RIA, at p. 66.

almost sure to shrink, meaning that net benefits will be relatively less negative, given they avoid the one-time compliance costs associated with the proposed rule. OEA assumes that the one-time compliance costs would be eliminated through these regulatory approaches because they largely exempt existing LDTs from premarket review, 510(k), and De Novo requirements.[82] Further, at least for the first of these two alternatives, OEA estimates that ongoing annual costs would be between 51 and 58 percent of those associated with the Proposed Rule.[83]

Presenting a full analysis of the benefits and costs of these alternatives should not be overly difficult for OEA, given that many of the elements of that analysis are already available. For example, considering the alternative that would exempt from premarket review requirements existing LDTs as well as new LDTs that have obtained New York State approval, the primary source of uncertainty would be in estimating the proportion of new LDTs that would opt for approval under New York's CLEP rather than FDA's premarket approval processes.[84] This information could be derived by comparing the relative costs of FDA and CLEP test approval, the latter of which is publicly available.

Even absent these data, a conservative analysis could simply assume, as OEA's existing discussion in the RIA suggests, that this alternative would not impose compliance costs on the proportion of LDTs that opt to submit to CLEP in the existing environment. Assuming the remaining LDTs would be indifferent between undergoing FDA or New York State approval processes, the analysis can proceed by developing the key elements associated with the analysis of the Proposed Rule for these remaining tests. This includes estimating the number of new LDTs that would be at risk and the associated health costs, the compliance costs imposed on those that would still be offered, and the benefits associated with FDA or New York State approval with regard to the possibility for fewer false negative tests.

B. Separately Evaluating the Distributional Effects of the Proposed Rule

Often those who bear the costs of a regulation are not the same as those who enjoy its benefits. Moreover, a simple focus on net benefits in an RIA does not allow a policymaker the ability to consider distributional effects in their decision calculus. To account for this, Circular A-4 directs agencies preparing RIAs to analyze the distributional effects of the proposed rule as well. The phrase "distributional effect" references the effect a proposed rule has on sub-groups of the population or economy, including groups divided by income, race, sex, industry, or geography.[85]

OEA's RIA offers limited discussion of distributional effects. The RIA does note that existing health inequities could be exacerbated or ameliorated. However, it fails to address with

[82] Proposed Rule RIA, at p. 101.
[83] Proposed Rule RIA, at p. 97.
[84] Proposed Rule RIA, at p. 102-3. With this alternative, OEA also considers the possibility that some laboratories might consider opting for FDA's Third Party review program for 510(k) submissions but suggests the fees are comparable to FDA's approval fees.
[85] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 14.

any specificity the sub-groups that are at risk.[86] Still, it seems clear that a disproportionate amount of the Proposed Rule's costs will be imposed on vulnerable individuals, including those with rare diseases, low-income individuals, and racial minorities.

If finalized, the Proposed Rule will lead to consolidation in the testing market and reduced competition as LDTs are forced to leave the market as they are no longer economically feasible. It is notable that the effect of the Proposed Rule on LDT prices receives limited attention in OEA's RIA, with brief qualitative discussions in only a few places in the document.[87] Yet, for the LDTs that can remain in the market, providers will be forced to raise prices to handle the additional burden of significant additional compliance costs to allow those LDTs to remain economically viable.

As prices rise for health care services, including diagnostic tests, the law of demand assures that a measurable decrease in demand will occur for those services (even for insured individuals).[88] Importantly, low-income individuals with higher price elasticities will bear more of the burden of the Proposed Rule by taking on more of the mortality costs from price increases, as they cut back on using medical services.[89]

Similarly, those patients that are uninsured will most feel the impact of higher prices and will be more likely to opt out of diagnostic testing. Rates of uninsurance disproportionately concentrate on minority individuals and communities. For example, the US Census estimates that 8.3 percent of Black and 17.9 percent of Hispanic individuals do not have insurance, relative to 4.9 percent for White individuals.[90] Perhaps those most at risk under the Proposed Rules are the vulnerable individuals that fall in subgroups of people with rare diseases. Lower volume tests will be most at risk of market exit, reduced competition, and price increases.

In light of the large compliance costs relative to the revenues of LDTs, to fulfill its obligations under Circular A-4, it would seem that OEA must evaluate the distributional effects of the Proposed Rule to a much greater extent than they currently do, taking into account declines in market access to LDTs and changes in demand for services from increases in prices. This is perhaps even more important given OIRA's recent emphasis on broadening participation in the regulatory process in response to President Biden's Executive Order 14094, especially among traditionally underserved communities such as those that will be significantly affected by the Proposed Rule.[91]

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[86] Proposed Rule RIA, at p. 106.
[87] Proposed Rule RIA, at p. 88-9, 106.
[88] Ellis, Randall P., et al. "Health Care Demand Elasticities by Type of Service." *Journal of Health Economics* (2017) 55: 232-243.
[89] See, e.g., Anderson, Michael, et al. "The Effect of Health Insurance Coverage on the Use of Medical Services." *American Economic Journal: Economic Policy* (2012) 4(1): 1-27.
[90] United States Census Bureau, Current Population Reports: Health Insurance Coverage in the United States: 2022 (September 12, 2023), available at census.gov/library/publications/2023/demo/p60-281.html.
[91] OMB, Request for Comments on Guidance Implementing Section 2(e) of the Executive Order of April 6, 2023 (Modernizing Regulatory Review), 88 FR 20916, (Apr. 7, 2023); Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023).

V. Conclusion

OEA's RIA to accompany FDA's Proposed Rule fails in certain important areas to adhere to best practices as described in OMB's Circular A-4, as well as the accompanying literature considering the application of benefit-cost analysis to regulatory issues, which has substantial implications for the resulting estimates of benefits, costs, and distributional effects. Specifically, the analysis fails to:

1) quantify key ancillary costs with available data;
2) select and interpret studies in a sound manner to apply benefit transfer;
3) consider and quantify the effects of reasonable regulatory alternatives; and
4) recognize and quantify key distributional effects.

These limitations of the RIA lead to an analysis that significantly overstates the likely benefits, substantially understates the likely costs, and minimizes the potential substantial distributional effects of FDA's Proposed Rule. Remedying these issues by employing approaches outlined in this letter, as well as others, will allow OEA's RIA to demonstrate more accurately whether the benefits of the Proposed Rule justify its costs, ascertain if alternative approaches could better achieve FDA's goals at a lower cost, and offer a more transparent account of the Proposed Rule's likely impacts on those affected and other interested parties.

EXHIBIT H

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Laboratory Developed Tests Final Rule

Docket No. FDA-2023-N-2177

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

Economics Staff
Office of Economics and Analysis
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

Executive Summary

This final rule amends FDA's regulations in part 809 (21 CFR part 809) to make explicit that "in vitro diagnostic products" (IVDs) are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(h)(1)) including when the manufacturer of the IVD is a laboratory. In conjunction with this amendment, FDA is phasing out its general enforcement discretion approach for laboratory developed tests (LDTs) so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs, as discussed further in section V of the preamble to the rule.

We quantify benefits to patients from averted health losses due to problematic IVDs offered as LDTs.[1,2] We focus mainly on certain broad disease categories associated with the majority of misdiagnosis-related harms in the U.S. Additional benefits include averted non-health losses from reduced spending on problematic IVDs offered as LDTs and unquantified reduction in costs from lawsuits. We quantify costs to affected laboratories for complying with statutory and regulatory requirements, as described in the phaseout policy. Additional costs include costs to FDA, which we include in our estimates. We estimate that the annualized benefits over 20 years range from $0.99 billion to $11.1 billion at a seven percent discount rate, with a primary estimate of $3.51 billion, and from $1.24 billion to $13.62 billion at a three percent discount rate, with a primary estimate of $4.34 billion. The annualized costs range from $566 million to $3.56 billion at a seven percent discount rate, with a primary estimate of $1.29 billion, and from $603 million to $3.79 billion at a three percent discount rate, with a primary estimate of $1.37 billion.

[1] See discussion of "problematic IVDs" in section I.B below.
[2] See discussion of "IVDs offered as LDTs" in section V.A.1 of the preamble to the final rule and section II.D below.

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Executive Orders 12866, 13563, and 14094 direct us to assess all benefits, costs, and transfers of available regulatory alternatives and to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Rules are "significant" under Executive Order 12866 Section 3(f)(1) (as amended by Executive Order 14094) if they "have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of [the Office of Information and Regulatory Affairs (OIRA)] for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities." OIRA has determined that this final rule is a significant regulatory action under Executive Order 12866 Section 3(f)(1).

Because this rule is likely to result in an annual effect on the economy of $100 million or more or meets other criteria specified in the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act, OIRA has determined that this rule falls within the scope of 5 U.S.C. 804(2).

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because most facilities that will be affected by this rule are defined as small businesses and the final rule is likely to impose a

substantial burden on the affected small entities, we find that the rule will have a significant economic impact on a substantial number of small entities.

We prepared an analysis consistent with the Unfunded Mandates Reform Act of 1995 (section 202(a)), which requires to the preparation of a written statement that includes estimates of anticipated impacts before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $177 million, using the most current (2022) Implicit Price Deflator for the Gross Domestic Product. This final rule will result in an expenditure in at least one year that meets or exceeds this amount.

B. Overview of Benefits, Costs, and Transfers

This final rule amends FDA's regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) including when the manufacturer of the IVD is a laboratory. As discussed in section V of the preamble to the final rule, FDA is phasing out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs.

We anticipate that the benefits of phasing out FDA's general enforcement discretion approach for LDTs includes a reduction in healthcare costs associated with unsafe or ineffective IVDs offered as LDTs (generally referred to in this document as "problematic IVDs"), including IVDs offered as LDTs that are promoted with false or misleading claims, and from therapeutic decisions based on unreliable results of those tests. Quantified benefits are the annualized sum of both health and non-health benefits. Unquantified benefits include, among others, possible

reduction in costs from lawsuits. We discuss the benefits of phasing out of FDA's general enforcement discretion approach for IVDs offered as LDTs in section II.E.

This phaseout policy will result in compliance costs for laboratories that are ensuring their IVDs offered as LDTs are compliant with statutory and regulatory requirements, as described in section V of the preamble. We discuss the costs of the phaseout policy in section II.F. These costs overlap somewhat with effects associated with this phaseout policy in the form of user fees, including annual registration fees, fees for premarket applications/submissions, and annual fees for periodic reporting concerning PMA-approved devices, which are paid from laboratories to FDA. These fees are paid by laboratories but are revenue for FDA; the approach to estimating fee effects is distinct from the approaches for either benefits or costs, so they will be presented as transfers. We discuss transfers in section II.H.

Table 1 summarizes the annualized benefits, costs, and transfers of the phaseout policy. At a seven percent discount rate, 20-year annualized benefits range from about $0.99 billion to $11.1 billion, with a primary estimate of $3.51 billion per year. At a three percent discount rate, 20-year annualized benefits range from $1.24 billion to $13.62 billion, with a primary estimate of $4.34 billion per year. At a seven percent discount rate, 20-year annualized costs range from about $566 million to $3.56 billion, with a primary estimate of $1.29 billion per year. At a three percent discount rate, annualized costs range from about $603 million to $3.79 billion, with a primary estimate of $1.37 billion per year. At a seven percent discount rate, 20-year annualized transfers range from $20 million to $81 million, with a primary estimate of $41 million per year. At a three percent discount rate, 20-year annualized transfers range from $29 million to $115 million, with a primary estimate of $58 million per year. These estimates do not include anticipated offsets from user fees. At a seven percent discount rate, 20-year annualized costs

to FDA range from $61 million to $243 million, with a primary estimate of $121 million per year. At a three percent discount rate, 20-year annualized costs to FDA range from $65 million to $259 million, with a primary estimate of $129 million per year. Factoring in offsets from user fees at current levels, estimated costs to FDA are reduced to $40 million to $162 million at a seven percent discount rate, with a primary estimate of $81 million, and to $36 million to $144 million at a three percent discount rate, with a primary estimate of $72 million, covering approximately 30 to 40 percent of the estimated costs to FDA.

Table 1. Summary of Benefits, Costs and Transfers (millions of 2022 U.S. dollars)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($m/year)	$3,509	$988	$11,096	2022	7%	20 years	Major sources of benefits will be the avoidance of harms to patients from use of problematic IVDs offered as LDTs and the avoidance of spending on such IVDs.
		$4,341	$1,244	$13,619	2022	3%	20 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized ($m/year)	$1,287	$566	$3,559	2022	7%	20 years	A portion of foreign costs will be passed on to domestic consumers. We estimate that up to $147 million in annualized costs (7%, 20 years) to foreign facilities could be passed on to
		$1,372	$603	$3,789	2022	3%	20 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
								domestic consumers.
Transfers	Federal Annualized Monetized ($m/year)	$41	$20	$81	2022	7%	20 years	The main portion of transfers will be user fees for premarket submissions.
		$58	$29	$115	2022	3%	20 years	
		From: Device Industry			To: FDA			
	Other Annualized Monetized ($m/year)					7%		
						3%		
		From:			To:			
Effects	State, Local, or Tribal Government: No significant effects Small Business: The phaseout policy will have a significant economic impact on a substantial number of small laboratories that manufacture IVDs offered as LDTs. Wages: N/A Growth: N/A							

C. Comments on the Preliminary Economic Analysis of Impacts and Our Responses

On October 3, 2023, FDA published the proposed rule Medical Devices: Laboratory Developed Tests (88 FR 68006). Accompanying the proposed rule was a comprehensive preliminary regulatory impact analysis (hereinafter referred to as the preliminary analysis or PRIA) on which we requested public comments (Ref. [1]). We received many comments and have organized these comments and our responses by topic in the paragraphs below. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value, importance, or the order in which it was received.

1. Comments (Number of Laboratories)

Comments suggested using data from the CMS Laboratory Registry which provides information on the number of laboratories in the United States and their accreditation status to estimate the number of laboratories affected by the rule.

Response: As mentioned in the PRIA, we acknowledge that we do not know the exact number of laboratories that will be affected by this rule. After reviewing comments, FDA revised the number of affected laboratories from 12,000 to 11,808 using data from the CMS Laboratory Registry. We still use information about laboratories in New York State (NYS) to estimate the percent of CLIA-certified laboratories that both comply with high complexity requirements and make IVDs offered as LDTs, assuming that NYS is representative of the U.S. laboratory community. We explain our revised estimate in greater detail in section II.D.1 and appendix A of this analysis.

2. Comments (Number of IVDs Offered as LDTs)

Some comments claimed FDA overestimated the number of IVDs offered as LDTs on the market while others claimed FDA underestimated this number. One comment stated that there are 160,000 IVDs offered as LDTs in the United States from 12,000 laboratories (or 13 IVDs offered as LDTs per laboratory). Other comments provided estimates of the number of IVDs offered as LDTs ranging from 92 to 310 IVDs offered as LDTs per laboratory.

Response: As mentioned in the preliminary analysis (section II.D.1), we acknowledge that some large reference laboratories may make a large number of new IVDs offered as LDTs per year, whereas smaller laboratories may focus on fewer IVDs overall and may not introduce many or any new IVDs each year. Using the additional estimates on the number of IVDs offered as LDTs received from comments, the weighted average estimate of the affected tests is calculated to be approximately 69 IVDs offered as LDTs per affected entity, which is close to

our original estimate of 67 IVDs offered as LDTs per affected entity[3]. We have not revised our estimate based on these data because the estimate did not change significantly.

However, we adjusted our estimate to reflect the enforcement discretion policies in the final phaseout policy as well as the Agency's intention to initiate the reclassification process for most IVDs that are currently class III (high risk) into class II (moderate risk).[4] FDA will also continue taking a risk-based approach in the initial classification of individual IVDs to determine the appropriate level of regulatory controls and whether a new test may be classified into class II through De Novo classification (and special controls established), rather than being class III and subject to the PMA pathway. Based on its experience, the Agency believes that special controls could be developed, along with general controls, that could provide a reasonable assurance of safety and effectiveness for most future companion diagnostic and infectious disease IVDs. As such they would be regulated as class II devices. As a result of this adjustment, and prior to additional adjustments to address enforcement policies, the estimated numbers of PMAs and PMA supplements submissions are lower while the estimated numbers of 510(k)s and De Novo submissions are higher after potential reclassification (see Table A.5). As the final phaseout policy includes an enforcement discretion policy with regards to QS requirements (except for requirements under 21 CFR part 820, subpart M (Records)) and premarket review requirements for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in certain limited ways as

[3] The new estimate of 69 IVDs offered as LDTs per affected entity was derived using comments and the initial PRIA estimate of 67. Specifically, we weighted together a maximum estimate of 310, a high estimate of 192, a middle estimate of 67, a low estimate of 13, and a minimum estimate of 1.

[4] FDA -CDRH Announces Intent to Initiate the Reclassification Process for Most High Risk IVDs. https://www.fda.gov/medical-devices/medical-devices-news-and-events/cdrh-announces-intent-initiate-reclassification-process-most-high-risk-ivds. As discussed in the preamble to the final rule, FDA notes that the reclassification process will include opportunities for public comment and FDA aims to complete the process before stage 4 of the phaseout policy.

described in the preamble, we expect that fewer IVDs offered as LDTs will be affected by stages 3 through 5 of the phaseout policy than we estimated in our preliminary analysis. In addition, FDA has revised the phaseout policy to include several other enforcement discretion policies for certain other types of IVDs (see section V.B of the preamble) and we have revised our estimates accordingly. Our updated estimates are addressed in sections II.F.3 and II.F.4 of this document.

3. Comments (Percent of IVDs That Are Offered as LDTs)

As discussed in section VI.C of the preamble, some comments claimed FDA overestimated the number of IVDs offered as LDTs on the market. Relatedly, comments suggested that the percent of test order volume for IVDs offered as LDTs is lower than 50%. One comment claimed that FDA's estimate of the number of IVDs offered as LDTs was more than "10 times what researchers found in a peer-reviewed study published in the American Journal of Clinical Pathology of actual clinical test orders at University of Utah Health: 3.9%" (see Ref. [3]). Another comment stated that only 6% of tests performed in their laboratory are offered as LDTs.

Other comments suggested that FDA underestimated the number of IVDs offered as LDTs on the market. Among these, a comment noted that their laboratory, itself part of an academic medical center, offers 123 LDTs out of 124 tests, a percentage higher than 99%. Another comment stated that more than 99% of their tests are LDTs, and further clarified that these tests comprised an even higher percent of their test volume.

Response: Based on public comments, the percent of IVDs offered as LDTs and the percent of test order volume comprised by such appear to vary widely across settings. Using test orders from a U.S. academic hospital system, Rychert et al. (2023) estimate that IVDs offered as LDTs are 3.9% of test order volume and 45% of distinct tests (Ref. [2]). Specifically for

estimating the percent of patients who are tested with IVDs offered as LDTs, we thus consider a range from 3.9% to 45%, with a primary estimate of 10%. This reflects the assumption that, while we take 45% as a reasonable estimate of the percent of IVDs that are offered as LDTs, we consider the percent of patients tested with those IVDs offered as LDTs to be closer to the referenced 3.9%, and, using professional judgement, selected 10% as our primary estimate, rather than using 3.9% directly, to reflect uncertainty given that the 3.9% was based on information for one single laboratory. Compared to the estimate of 50% used in the preliminary analysis, the revised estimate of 10%, if holding all else equal, reduces estimated benefits by a factor of five. With respect to the analysis in section II.E.2, this reflects that order volume likely better represents distinct patients.

4. Comments (Attribution of Diagnostic Error to Analytic Phase of Laboratory Tests)

Comments suggested that the percent of diagnostic errors attributable to faulty diagnostic test results is likely lower than 50%, the estimate we used in the preliminary analysis. A comment suggested instead, based on published literature, a range of 1-4%, with a central estimate of 2.5% (Refs. [3], [4], [5], [6], [7], [8], [9], [10]).

Response: Our final analysis uses an updated methodology which no longer directly estimates this parameter. However, our range of estimates of the number of diagnostic errors attributable to faulty tests and resulting in harm is consistent with much rarer attribution of diagnostic errors to tests. This analysis estimates in total about 53,000 annual preventable harms attributable to diagnostic tests (the sums of the primary estimates of avoidable harms across Table 5, Table 11, and Table 14). Singh et al. (2014) estimate that approximately 12 million U.S. adult patients experience diagnostic errors in outpatient care every year (Ref. [11]). Our primary estimate thus represents about half a percent of this total. As our estimate of preventable harms

attributable to diagnostic tests would represent a still lower percentage of all diagnostic errors (including those occurring in settings other than outpatient care), we do not consider this estimate inconsistent with attribution rates suggested in public comment.

5. Comments (Percent of IVDs Offered as LDTs that are Problematic)

Comments stated that the percent of IVDs offered as LDTs that are problematic is likely much lower than 47%, the estimate we used in the preliminary analysis. Comments also suggested that it is inappropriate to extrapolate this parameter from as narrow a sample as cited in the preliminary analysis.

Response: We agree that a broader basis for estimating this parameter is appropriate and have revised the relevant analysis accordingly, as described in detail in section II.E.1.a "Cancer: Mortality Risk." Using statistics from the NYS Department of Health Clinical Laboratory Evaluation Program (CLEP) (Ref. [12]) and FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests, [5] we consider a range of scenarios in which 22%, 38%, and 54% of IVDs offered as LDTs without FDA oversight would be a problematic IVD. This was extrapolated to estimate that 22%, 38%, and 54% of patients tested with IVDs offered as LDTs would be tested with problematic IVDs. Compared to the estimate of 47% used in the preliminary analysis, the revised primary estimate of 38%, if holding all else equal, reduces estimated benefits by approximately one fifth.

6. Comment (IVDs Offered as LDTs Perform Better Than FDA-Authorized[6] Tests)

[5] Memorandum to File from Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, RE: Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2 (September 22, 2023), available in Docket No. FDA-2023-N-2177.

[6] For purposes of this analysis, "FDA-authorized" refers to FDA permitting the marketing of a device via the premarket approval, 510(k), De Novo classification, BLA, or HDE pathway and to devices that are exempt from premarket notification. This term does not include devices authorized for emergency use under section 564 of the FD&C Act.

As further detailed in section VI.C.4 of the preamble, some comments pointed out omission of multiple publications claiming comparable or better performance of IVDs offered as LDTs compared to "FDA IVDs." Some comments suggested that patients would lose access to IVDs offered as LDTs that perform well, even some IVDs offered as LDTs that may perform better than FDA-authorized IVDs. Comments also suggested adjusting downwards our estimates of benefits from avoiding preventable misdiagnosis-related harms by subtracting harms from baseline problems of FDA-authorized tests.

Response: We do not agree that IVDs offered as LDTs generally perform comparably to or better than FDA-authorized tests. Thus, we do not agree that this analysis should reflect such a situation. Concerning the scientific merits of the claims in these comments, please refer to FDA's responses in section VI.C.4 of the preamble, "Evidence of the Need for Greater FDA Oversight." In particular, we discuss publications purported to compare the performance of IVDs offered as LDTs and FDA-authorized tests in our response to Comment 34.

With respect to estimating the difference in reliability between problematic IVDs offered as LDTs, specifically, and FDA-authorized competitor tests, we lack systematic data on the exact issues with all problematic IVDs offered as LDTs and their particular uses in the process of diagnosis. As described in section II.E.1.a "Cancer: Mortality Risk," we consider a range of rates at which avoidable diagnostic error might result from usage of problematic IVDs offered as LDTs that would not occur using an FDA-authorized test.

7. Comments (Effectiveness of FDA Review in Assuring Reliability of Diagnostic Tests)

Citing examples of FDA-authorized tests with alleged issues affecting reliability, comments suggested that our analysis of the proposed phaseout policy overestimated the

effectiveness of FDA review in assuring the reliability of diagnostic tests and reducing the use of problematic IVDs offered as LDTs.

Response: Unlike in our preliminary analysis, as explained in section II.E.1.a, we now use statistics from the NYS CLEP to inform our estimates of avoidable problematic IVDs offered as LDTs. We believe this is a relevant extrapolation to expected detection of reliability issues through FDA oversight.

8. Comment (Diagnostic Tests Only a Part of Diagnosis)

One comment expressed concern that FDA does not consider that the risks of IVDs offered as LDTs, including erroneous results, "is mitigated by the fact that they are part of a multi-faceted medical assessment and are rarely used in isolation for clinical decision-making."

Response: Due to uncertainty about the rate at which erroneous test results lead to erroneous treatment decisions, this analysis considers that inaccurate results might be identified during follow-up or other parts of the process of diagnosis before leading to harm from diagnostic error. As described in section II.E.1.a "Cancer: Mortality Risk," we consider a range of rates at which avoidable errors might result from usage of problematic IVDs offered as LDTs that would not occur using an FDA-authorized test. However, although for the purpose of this analysis we consider a wide range for these rates, FDA expects that erroneous test results often result in erroneous treatment decisions. As discussed in the response to Comment 6 in the preamble, FDA does not consider all clinicians to be aware of the limitations of tests. FDA routinely consults with healthcare providers and has encountered many who do not understand the limitations of tests and do not consider that a test result provided by a test may be incorrect. For additional discussion of this comment please see our response to Comment 6 in the preamble.

9. Comments (StatinCheck Problem)

Comments requested an explanation of why we included, in the preliminary analysis, the StatinCheck test for KIF6 genotype as an example of a problematic test.

Response: This test was marketed as a way to predict the risk of heart disease and determine a patient's response to statin drugs, based on the belief that patients with the Trp719Arg polymorphism of the KIF6 protein had an elevated risk of cardiovascular disease (CVD) events and would have a greater reduction in CVD events when on statin therapy than patients without this polymorphism. However, the results from studies of the association between the polymorphism, CVD risk, and statin response were conflicting, and multiple scientific publications reported no association between the polymorphism and elevated CVD risk or statin response (Refs. [13] [14]). Accordingly, the totality of scientific evidence does not support that there is a clinically valid relationship between the polymorphism, elevated CVD risk, and statin response. In 2011, FDA informed the manufacturer that its submission for premarket approval of this test was not approvable stating that the evidence submitted was insufficient to support the test's safety and effectiveness in determining risk of heart disease or in predicting statin response. As described in FDA's 2015 report, additional problems included that the test was incorrectly validated and marketed for unproven uses. Inaccurate assessment of patient risk or likelihood of responding to statin therapy could lead to overtreatment, with an associated risk of adverse events, as well as undertreatment, with the risk of failing to prevent CVD events and death.

10. Comments (Non-Invasive Prenatal Screening Tests Require Follow-Up)

As detailed in section VI.C of the preamble, FDA received comments regarding FDA's use of a New York Times article on NIPS as evidence of a problem (Ref. [15]). Specifically,

comments stated that the article conflated screening with diagnostic testing. They asserted that the article mischaracterized false positive results as test failures and that the "problem" with this category of tests is with "the lack of understanding of its purpose and limitations by the providers and patients who were interviewed by the reporters."

Response: FDA agrees that NIPS tests, which may tell people the risk of their fetus having certain genetic abnormalities, are different from diagnostic tests used to more definitively confirm or rule out a suspected genetic abnormality. FDA agrees with comments that NIPS tests should not be used to confirm or rule out a suspected abnormality. While higher false positive rates are often more acceptable for screening tests than tests used for making a diagnosis, appropriate false positive rates for any particular test needs to be considered in the context of a full benefit-risk evaluation for that particular test. After publication of the New York Times article, FDA issued a safety communication to explain the limitations of NIPS tests and provide information to educate both patients and health care providers to help reduce the inappropriate use of NIPS tests.[7] Increased oversight of NIPS tests, including labeling requirements, can help ensure such tests are appropriately labeled with transparent information regarding performance, clear instructions, and appropriate limitations. Including the example of NIPS in this final analysis reflects our expectation that phasing out the enforcement discretion approach will ensure tests are appropriately safe and effective for their intended use. We also expect truthful, accurate, and clear statements about test use and performance to prevent patient and provider misunderstanding.

11. Comments (Innovation)

[7] Available at: https://www.fda.gov/medical-devices/safety-communications/genetic-non-invasive-prenatal-screening-tests-may-have-false-results-fda-safety-communication

FDA received comments stating that the phaseout policy will have a negative impact on innovation in the testing space, as laboratories working to come into compliance would be either unable or unwilling to engage in innovative test development. Some comments stated that the regulatory constraints associated with the phaseout policy would cause laboratory manufacturers to develop fewer tests, hindering the timely development and deployment of cutting-edge therapies and diagnostic tools and ultimately harming patients. A comment from the Association of Pathology Chairs (APC) stated that it had conducted a survey of its members and found that 92% (36/39) of APC survey respondents reported that there will be less innovation to create and offer new tests to improve patient care due to the FDA's proposed phaseout policy. Comments claimed that the high cost of premarket review may lead to less investment in innovation, fewer new tests developed, and longer timelines for new innovation to reach the market, and that some tests may not have market viability, given the premarket review costs.

Several comments noted that laboratories must be able to modify existing tests quickly to diagnose new conditions and monitor the impact of new therapies. Some comments stated that stifling modifications of currently marketed IVDs offered as LDTs would force pathologists and other healthcare providers to use older, less optimal tests, and noted that many patients do not have the time to wait for diagnostic development and rely on laboratories to be nimble and adapt to changing diagnostic criteria. One comment asserted that predetermined change control plans (PCCPs) would not help alleviate delays in modifications because only manufacturers can submit PCCPs, and thus laboratories seeking to modify an IVD for local conditions would need to undertake premarket review to do so. One other comment expressed concern that the phaseout policy would lead to slowed growth in the number of LDTs manufactured by laboratories because the phaseout policy would "prohibit" labs from sharing their discoveries about such

IVDs with each other. This comment claimed that the sharing of this knowledge in the past had caused quicker development and modification of IVDs offered as LDTs.

Response: As explained in the preamble to the final rule, the phaseout policy is intended to better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs -- while also accounting for other important public health considerations such as patient access and reliance.

Premarket review is not required for all IVDs offered as LDTs. FDA premarket review is required only for certain tests (generally those in class II or class III). FDA estimates that approximately 50 percent of IVDs offered as LDTs will not require premarket review. A manufacturer's modifications to tests that have already been cleared, approved, or granted marketing authorization by FDA only require FDA review in certain circumstances (see 21 CFR 814.39; 21 CFR 807.81(a)(3)). Even when premarket review is required for an IVD offered as an LDT, FDA does not agree that such review necessarily impairs innovation. In fact, sponsors have sought and obtained FDA authorization for innovative IVDs offered as LDTs. FDA also has several programs that may facilitate the development and premarket authorization of innovative tests.

Moreover, better assuring the safety and effectiveness of IVDs offered as LDTs will foster innovation. By applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs, FDA's phaseout policy will remove a disincentive for non-laboratory manufacturers to develop novel tests. We anticipate that phasing out the general enforcement discretion approach for LDTs will spur innovation for IVDs for which there is a reasonable assurance of safety and effectiveness.

12. Comments (Impact on Prices)

Several comments stated that ending the general enforcement discretion approach for LDTs would lead to higher prices for clinical tests due to the costs of complying with applicable FDA requirements. Some comments further stated that the cost of complying with applicable requirements would result in the closure of many laboratories or the outsourcing of certain laboratory tests, which in turn will increase the costs of tests due to decreased test availability, decreased market competition, increased handling costs (e.g., costs associated with shipping samples to a centralized laboratory), or supply chain contractions. One comment expressed skepticism regarding FDA's statement that any losses may be offset by the market entry of IVDs from other manufacturers. FDA also received a comment which argued that increased prices for clinical tests will disincentivize people from seeking preventive care until they suffer an emergency, which will increase costs for the overall healthcare system. Collectively, these comments suggested that laboratories will pass increased costs to their customers, which some comments noted could result in higher insurance premiums. However, one comment stated that insurance companies will be more likely to cover tests (because they will have FDA authorization), which may allow for greater access to more affordable testing. One comment noted that it is inaccurate to assume that IVDs offered as LDTs are always cheaper.

Response: FDA recognizes that some laboratories may pass the costs of compliance with applicable requirements, including the specific examples listed in the comments, to their customers by raising prices for IVDs offered as LDTs. We also recognize that if many laboratories reduce operations or exit the market, production may be concentrated in a few large laboratories, which may cause prices for certain IVDs offered as LDTs to increase. However, we note that in the final phaseout policy, which will also affect small laboratories and Academic

Medical Centers (AMCs), there may be less laboratories that scale back operations or exit the market relative to the estimates in our preliminary analysis.

FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under 21 CFR 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in certain limited ways as described in the preamble. FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP.[8] FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements (except for requirements under 21 CFR part 820, subpart M (Records)) for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. These enforcement discretion policies may significantly reduce the costs of compliance under the final phaseout policy, thus reducing the number of laboratories that scale back operations or exit the market. In addition, we anticipate that FDA oversight could help to support coverage and reimbursement determinations for IVDs offered as LDTs, which we anticipate will make certain IVDs offered as LDTs for which there is a reasonable assurance of safety and effectiveness more affordable for patients. As a result, FDA does not agree that patients will necessarily be disincentivized from seeking preventive care resulting in increased costs to the healthcare system as a result of the phaseout policy.

[8] Throughout this document, FDA uses the phrase "LDTs approved by NYS CLEP" to refer to LDTs that are approved, conditionally approved, or within an approved exemption from full technical documentation, under NYS CLEP. These three categories of LDTs are discussed further in section V.B.2 of the preamble. Other LDTs, including "LDTs used in Clinical Trials" and "Tests Not Subject to Evaluation" which are described on NYS CLEP's website, are not considered "LDTs approved by NYS CLEP" and are not within the enforcement discretion policy with respect to premarket review requirements described in section V.B.2 of the preamble. For additional discussion of the NYS CLEP premarket review program, see section V.B.2 of the preamble.

In addition, phasing out the general enforcement discretion approach for LDTs will help to reduce other healthcare costs. Greater oversight by FDA will help to address the hidden costs associated with unsafe or ineffective IVDs (including IVDs promoted with false or misleading claims), such as costs incurred from inappropriate treatments, additional or repeat testing, unnecessary consultations with providers, or additional treatment that became necessary due to the progression or worsening of a disease or condition following misdiagnosis. While certain costs may be passed on to individuals and insurers, we expect some of these costs will be offset by the associated benefits.

13. Comments (Increased Labor Cost/Strain)

FDA received comments expressing concern that phasing out the general enforcement discretion approach for LDTs would require laboratories to have increased resources to afford the necessary staffing and other costs related to test development and regulatory submissions and emphasized the thin financial margins with which small laboratories operate. Some comments stated that the impact on small laboratories will result in a loss of expertise and infrastructure. In addition, comments noted that such centralization of IVDs offered as LDTs at large laboratories may negatively impact medical education and training in pathology, resulting in labor shortages. Some comments also suggested that workforce shortages will make it difficult for FDA to recruit and retain adequate numbers of qualified reviewers trained in laboratory diagnostics needed to review premarket submissions, which could potentially lead to delays in FDA's premarket review process and patient access to tests.

Response: FDA appreciates the concerns regarding financial and administrative challenges for smaller laboratories. FDA anticipates that the enforcement discretion policies discussed in section V.B of the preamble will sufficiently address these concerns and help to

avoid undue disruption to the testing market. For example, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements (except for requirements under 21 CFR part 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in section V.B.3 of the preamble, which means laboratories would generally not need to dedicate staff or resources to handle premarket submissions for their existing IVDs offered as LDTs.

It is possible that some laboratories could need additional staff to handle premarket submissions for new IVDs and we account for this in our analysis. However, we expect that FDA's enforcement discretion policy for currently marketed IVDs offered as LDTs will greatly reduce the volume of submissions from the estimate in our preliminary analysis, thereby avoiding any sudden or drastic increase in labor costs.

14. Comments (Underestimation of Costs)

Several comments stated that costs are substantially underestimated. Some comments elaborated on specific types of costs, especially costs of premarket review. In support of their arguments some comments provided cost estimates for premarket review per entity while others provided cost ranges per test including analytical and clinical validation costs. Another comment focused on how the cost of modifying an SOP could be more burdensome than estimated as it would have to occur for every IVD offered as an LDT. Some comments also conveyed concern that the cost of a possible increase in LDT outsourcing due to FDA's phaseout of enforcement discretion were not considered. Several comments stated that the costs of hiring new labor to comply with the phaseout of enforcement discretion was underestimated.

Response: FDA has revised the phaseout policy to include several enforcement discretion policies for certain types of IVDs as described in section V.B of the preamble. For example, FDA intends to exercise enforcement discretion for premarket review and QS requirements (except for requirements under 21 CFR 820, subpart M (Records)) for IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule and that are not modified, or that are modified as described in the preamble. As such, we do not expect that premarket submissions will be submitted for most currently marketed IVDs offered as LDTs in the immediate future, thus reducing the costs of the phaseout policy including the costs of premarket submission and review. We have revised our estimates consistent with revisions to the phaseout policy as explained in section II.F of this analysis.

15. Comments (Outsourcing Costs and Costs of Switching to FDA-Authorized Tests)

Some comments stated that if FDA phases out the general enforcement discretion approach for LDTs, the commenters may decide to switch from an IVD offered as an LDT to an FDA-authorized test or to outsource their tests to other laboratories. Some comments provided information about the cost differential between an IVD offered as an LDT and an FDA-authorized test or from outsourcing certain tests. Some comments provided estimates on the number or percentage of tests that they would consider outsourcing or switching to an FDA-authorized test.

Response: FDA has revised the phaseout policy to include several enforcement discretion policies for certain types of IVDs as described in section V.B of the preamble. For example, FDA intends to exercise enforcement discretion for premarket review and QS requirements (except for requirements under 21 CFR 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final

rule and that are not modified, or that are modified as described in the preamble. As such, we generally do not expect laboratories with currently marketed IVDs offered as LDTs to switch from an IVD offered as an LDT to an FDA-authorized test or to outsource their tests to other laboratories. We agree, however, that some laboratories may pursue outsourcing their testing needs or switching to use of an FDA-authorized test rather than introducing a new test, that does not fall within an enforcement discretion policy in the phaseout policy. However, as we explain in section II.F.6. of this FRIA, the cost of switching to an FDA-authorized test when available, would cost less than the cost of submitting a premarket submission. A laboratory would likely switch to FDA-authorized tests or outsource their testing needs only if submitting a premarket submission was more costly than either of these alternatives. Either way, the decision would be a private decision made according to their business plan. To the extent that any number of laboratories switch to any number of FDA-authorized tests, their costs would be less than the costs of submitting a premarket submission.

16. Comment (FDA Would Not Have Sufficient Resources To Review IVDs Offered as LDTs)

Some comments expressed concerns that FDA would not have sufficient resources to conduct timely premarket review of IVDs offered as LDTs to meet the public health needs. Some of these comments questioned whether FDA would have adequate capacity to provide timely review of applications/submissions for IVDs offered as LDTs because many EUA requests were not reviewed due to resource limitations during the COVID-19 pandemic. At least one comment cited FDA's review of a particular EUA request for an LDT during the COVID-19 pandemic, in which FDA's review of the request did not conclude until after the subject LDT had been removed from the market, as proof that FDA does not have adequate resources to conduct

premarket review of IVDs offered as LDTs. Another comment referenced a supposed FDA delay in recognizing a particular consensus standard, based on FDA's "prolonged review."

Other comments referenced FDA's MDUFA IV performance report from FY2020 to 2022 (during the COVID-19 pandemic) and predicted that the increased volume of submissions from laboratory manufacturers that would result from the phaseout policy would affect FDA's overall ability to review premarket submission for all IVDs, meet its MDUFA performance goals, and conduct other essential work, including policy and post-market activities. Finally, some comments recommended that FDA modify the phaseout policy to prolong the period of time prior to phasing out the general enforcement discretion approach with respect to premarket review requirements, and/or continue to apply the general enforcement discretion approach with respect to premarket review requirements for certain LDTs, to reduce the FDA resource needs.

Response: FDA disagrees that the Agency will lack sufficient resources to conduct premarket review of IVDs offered as LDTs in a timely manner. First, FDA does not intend to phase out the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs until 3½ years after publication of the phaseout policy, and for moderate- and low-risk IVDs (that require premarket submissions), until 4 years after publication of the phaseout policy. This timeline aligns with the next reauthorization of MDUFA. This alignment will provide an opportunity for FDA and industry to negotiate regarding user fees and performance goals with the knowledge that laboratory manufacturers will be expected to comply with applicable premarket review requirements.

Second, FDA generally intends to exercise enforcement discretion with respect to certain requirements for certain tests as described in the final phaseout policy. These enforcement discretion policies are discussed further in section V.B of the preamble and collectively will

significantly reduce the number of premarket submissions for IVDs offered as LDTs, as compared to our preliminary estimates.

Third, FDA's device authorities require premarket review only for certain IVDs. FDA estimates that approximately 50 percent of IVDs currently under active oversight are low risk and do not require premarket review, and FDA assumes this estimate also applies to IVDs offered as LDTs (see section II.F.2.c of this analysis). However, there are uncertainties surrounding the estimate of total numbers of IVDs offered as LDTs on the market because FDA generally has not enforced the registration and listing requirements for LDTs under section 510 of the FD&C Act (21 U.S.C. 360), 21 CFR part 607, and 21 CFR part 807 (excluding subpart E). By 2 years after publication of this final rule, at stage 2 of the phaseout policy, FDA will obtain registration and listing information from laboratory manufacturers offering IVDs as LDTs. This information will help FDA assess and plan for the resources needed for premarket review of those IVDs before stages 4 and 5 of the phaseout policy.

Fourth, FDA is currently working to enhance its 510(k) Third Party Review Program to handle the review of low- and moderate-risk devices by recognized Third Party review organizations. This will free up Agency staff time to review more complex, innovative, high-risk devices. FDA estimates that half of the IVDs offered as LDTs for which a 510(k) will be submitted will be reviewed under the Third Party review program. FDA also recognizes that if CLIA accreditation organizations seek accreditation under FDA's Third Party review program, there may be certain efficiencies or other advantages, because the two programs are complementary, as described in response to Comment 7 of the preamble. FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP and to generally not enforce requirements for LDTs

manufactured and performed within the Veterans Health Administration (VHA) and the Department of Defense (DoD). See section II.G of this analysis.

Finally, FDA disagrees that decision timelines on EUA requests, in general, are a good indicator to predict FDA's timelines for review of premarket applications/submissions for IVDs offered as LDTs, and further disagrees that FDA's review of any one particular EUA request submitted for an LDT during the COVID-19 pandemic is indicative of how FDA will review premarket applications/submissions for IVDs offered as LDTs generally. As discussed in response to comment 275 in the preamble, FDA's authority to issue EUAs for LDTs is under a different statutory provision (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)) than traditional premarket reviews. Moreover, FDA is not required to review individual EUA requests submitted to FDA or review them on a specific timeline, or to authorize the emergency use of a medical product even if it meets the relevant criteria for an EUA, giving FDA flexibility to determine how to prioritize its efforts in emergencies to protect and promote public health. Second, during the COVID-19 pandemic, FDA received a large influx of submissions that had not been anticipated. In the context of the phaseout policy, FDA has estimated the number and type of premarket submissions we can expect in Stages 4 and 5, and annually thereafter, and can prepare for those submissions. See our responses to comments 37 and 275 in the preamble for additional discussion on this topic.

17. Comment (Small Entities)

As discussed in section VI.G of the preamble, FDA received comments expressing concern that phasing out the general enforcement discretion approach for LDTs will put financial and administrative pressure on small laboratories. These comments state that the phaseout of general enforcement discretion could result in laboratory closures and potential monopolies in

the testing space. Several comments stated that large laboratories will be able to monopolize LDT processing as they have the resources to afford the necessary staffing and other costs related to test development and regulatory submission. One comment discussed small laboratories within a medical system closing, stating that the removal of pathologists due to this kind of laboratory exit would decrease the quality of patient care.

Response: FDA appreciates the concerns regarding financial and administrative challenges for smaller laboratories. Specifically, FDA recognizes that smaller laboratories may face an increase in total cost such that they will exit the market and potentially cause increased testing market concentration. The extent in which smaller laboratories may be disproportionately impacted by the phaseout of the general enforcement discretion approach for LDTs, is dependent on the number of IVD's offered as LDTs per lab. FDA anticipates that the enforcement discretion policies discussed in the preamble of the final rule will moderate these concerns and help to avoid complete disruption to the test market. As noted in Appendix B – Table 8, the average costs per LDT are smallest for stages 1 through 3 of the phaseout policy representing 10% of costs and up to 59% of affected tests, whereas average costs per LDT for stages 4 and 5 represent 90% of costs affecting 3% of tests. The percentage of tests that may experience costs under stages 4 and 5 will increase as new laboratories and tests enter the market during and after stages 4 and 5, as they will fall within the enforcement discretion policy for currently marketed tests. However, they may still fall within the scope of other enforcement discretion policies described in the preamble to the final rule, including those for unmet needs and LDTs approved by NYS CLEP. However, in the event that a new lab does not fall within the scope of other enforcement discretion policies, costs under stages 4 and 5 could present as a potential barrier to entry in the LDT market for new laboratories. In Table B.7, total costs and

transfers for all stages of the phaseout policy are estimated to be on average anywhere between 2.5, 5.8 and 16 percent over receipts for all entities. We do not have the information about labs to determine how the average estimates are distributed among the firms (including new firms) according to their size categories. Also, costs would be higher for a lab that has several IVDs offered as LDTs but sells fewer unit tests whereas costs would be smaller for labs with only one IVD offered as LDTs selling a large number of unit tests. In the same manner, profit margins could be higher for labs with a smaller number of IVDs offered as LDTs but with high volume unit tests sold, compared to labs with a larger number of IVDs offered as LDTs but with low volume units tests sold. Depending on profit margins with respect to revenue, the costs of this rule may be prohibitive for some small labs, making it more likely that some small entities in this size category will exit the market, reduce operations, sell the business, be subject to acquisitions by larger firms or not enter the market. If profit margins were too small for many small firms considering the costs, it is possible that this rule will be too burdensome for some small entities.

While we do not have the data on profit margins to properly estimate the number of labs that would be adversely impacted by this rule, we estimate that small laboratories make fewer IVDs offered as LDTs than large firms. We estimate that small labs make up 92 percent of all labs, and that they also hold a 24 percent share of IVDs offered as LDTs. With the low number of IVDs offered as LDTs per small lab, it is more likely that the percent of costs over receipts per lab would be closer to our low average estimate 2.7 percent.

With the above referenced revisions to the phaseout policy, we do not expect significant disruptions to access to IVDs offered as LDTs, significant increases in test prices, or delays in diagnosis and treatment. However, the high cost of pre-market approval also makes innovation less likely to come from smaller labs.

18. Comment (Firm Exit and Market Concentration)

Some comments have claimed that certain laboratories, such as academic, small, public health, and specialty laboratories, will disproportionately exit the market relative to their counterparts. These comments claim that since these labs already have low revenues, any additional cost could be enough to cause market exit.

Other comments stated that by reducing the availability of IVDs offered as LDTs through market exit, the phaseout policy would lead to delays in testing, including by potentially increasing reliance on reference laboratories which may increase the time individuals obtained test results. Some comments expressed concern that the laboratories surviving general enforcement discretion phaseout would receive an influx of test orders and may not be able to handle the test volume, which may have an overall negative impact on the turnaround time for test results. Two comments have addressed the exit of academic labs as particularly concerning given their role in diagnosing and monitoring rare diseases. Further, many comments stated that a potential increase in firms exiting the market could increase unemployment among laboratory technicians and increase market concentration in the healthcare industry.

A few comments also addressed children's hospital laboratories as particularly likely to be negatively affected by the phaseout policy. These comments stated that because these hospitals rely largely on Medicaid payment, the laboratories in these hospitals may have small revenue levels and may reduce their IVD offerings, exit the market, or send samples to other laboratories for testing if the total cost increase for meeting applicable requirements that result from the phaseout policy is too high.

Response: FDA appreciates the comments on potential firm exit and market concentration as a result of the phaseout policy. Given that FDA intends to exercise enforcement

discretion and generally not enforce premarket review and QS requirements (except for requirements under 21 CFR 820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule and that are not modified, or that are modified as described in the preamble, and for LDTs developed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system (as described in section V.B.3 of the preamble), we do not expect significant market concentration and firm exit to result from the phaseout policy. With the above referenced revisions to the phaseout policy, we also do not expect current disruption to access to IVDs offered as LDTs, significant increases in test prices, or delays in diagnosis and treatment.

D. Summary of Changes from the Proposed Rule

Compared to the preliminary economic analysis, this final analysis reflects revisions to the phaseout policy and to our analytical methodology. We include updates and revisions to our discussion of baseline conditions, estimated health and non-health benefits, costs, budgetary impacts, transfers, regulatory alternatives, and impacts to small entities as summarized below.

1. Changes to the Phaseout Policy

The final phaseout policy differs significantly from the proposed policy in that it includes the following additional enforcement discretion policies:

- FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements, with the exception of requirements under 21 CFR part 820, subpart M (Records), for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified in certain limited ways as described in section V.B.3 of the preamble.

- FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP;
- FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements and QS requirements, with the exception of requirements under 21 CFR part 820, subpart M (Records), for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system;
- FDA intends to exercise enforcement discretion and generally not enforce requirements for LDTs manufactured and performed within the Veterans Health Administration (VHA) or the Department of Defense (DoD); and
- FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements, with the exception of requirements under 21 CFR part 820, subpart M (Records), for non-molecular LDTs for rare red blood cell antigens where such tests are manufactured and run in transfusion services and immunohematology laboratories and where there is no alternative available to meet the patient's need for a compatible blood transfusion.

Where relevant, we adjust estimates in this final analysis in accordance with these changes to the phaseout policy. More details of IVDs within the scope of the phaseout policy are described in section V.A of the preamble.

2. Baseline Conditions

After reviewing comments, FDA revised the number of laboratories affected by the phaseout policy using data from the CMS Laboratory Registry as explained in appendix A.

Using the CMS data, the revised primary estimate of affected laboratories is 1,181, which is close to the estimate of 1,200 in the preliminary analysis.

3. Benefits

We have made several changes to our analysis of health benefits. While there are individual changes that increase as well as decrease estimated benefits, overall total estimated benefits have decreased due to incorporating new information and assumptions. However, while including data and information from public comments as well as additional research has lowered estimated annualized benefits from expected reductions in cancer mortality to about one fiftieth of the preliminary estimate, we now also use this information to quantify benefits that we previously discussed qualitatively or only addressed incompletely. In particular, we now include general, yearly estimates of mortality avoidable in cardiovascular disease and morbidity avoidable in infectious diseases.

In response to comments, and as described in section II.E.1.a of this analysis, we have revised our methods for estimating avoidable harms related to cancers. We have also applied revised methods in newly estimating avoidable harms related to cardiovascular and infectious diseases. Revisions concern both reference information and analytical assumptions.

We now source certain parameters addressed in public comments, such as the rate of usage of IVDs in cancer, cardiovascular diseases, and infectious diseases, from published literature and other data. Additionally, we now estimate the rate of usage of problematic IVDs offered as LDTs based on application review statistics from the NYS Department of Health Clinical Laboratory Evaluation Program (CLEP) (Ref. [12]) and FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests.[9]

[9] Memorandum to File from Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, RE:

We have also refined analytical assumptions. For example, although we did not assume in the preliminary analysis that 100% of uses of problematic IVDs offered as LDTs result in a harm from diagnostic error, we have refined our assumptions to avoid any implication that this is the case.

Due to our high degree of uncertainty about several of the parameters used to estimate health benefits, we now use Monte Carlo simulations to determine a plausible range for benefits pertaining to each disease category by allowing parameters to vary independently of each other. Not using such an approach would implicitly convey a strong and unrealistic assumption that all uncertain parameters share a joint probability distribution and are perfectly dependent (i.e., aligning all best- and worst-case scenarios across parameters).

With respect to non-health benefits, we have removed discussion and estimates made in section II.E.3 of the Preliminary Regulatory Impact Analysis (PRIA) (Ref. [1]) where we had previously requested supporting information in public comment and did not receive any. Additionally, we have edited discussion for clarity, in part to address certain public comments.

Finally, as described in sections II.E.1 and II.E.3, we adjust estimates of benefits to account for existing review by NYS CLEP and the enforcement discretion policy for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule.

4. Costs

We have made several changes to our cost analysis. We use updated data for wages, FDA costs, and MDUFA fees. We made the following revisions as a result of changes to the final phaseout policy: exclude currently marketed IVDs offered as LDTs that were first marketed prior

Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2 (September 22, 2023), available in Docket No. FDA-2023-N-2177.

to the date of issuance of the final rule from premarket review and QS (except for records) compliance costs; exclude LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system from premarket review and QS compliance costs (except for records); and exclude LDTs expected to be reviewed by NYS CLEP from premarket review compliance costs. We also consider that some of the IVDs currently classified in class III, requiring PMAs/PMA supplements, may be reclassified to Class II or Class I (described in Appendix A and section II.F.4).

We have revised our estimates of FDA review costs to adjust the FTE weight of PMA review costs, to include review costs of MDRs, IDEs, and Q-submissions, and to consider premarket submissions that will be reviewed by third party or NYS CLEP (see section II.G). We have also refined some estimates in the analysis based on data received in public comments.

5. Regulatory Alternatives

The section on regulatory alternatives in the final analysis retains only the first two regulatory options from the preliminary analysis. For the final analysis, we include as an additional alternative the phaseout policy as initially proposed. See section II.J.

II. Final Economic Analysis of Impacts

A. Background

In 1976, the Medical Device Amendments (MDA) amending the FD&C Act created a comprehensive system for the regulation of devices intended for human use, including IVDs. Since 1976, FDA has considered IVDs to be devices within the meaning of the device definition in the FD&C Act (see section 201(h)(1) of the FD&C Act (21 U.S.C. 321(h)(1)); 21 CFR

809.3(a)). However, in implementing the MDA since 1976, FDA has exercised enforcement discretion such that it generally has not enforced applicable legal requirements with respect to most LDTs because they mostly:

- were manufactured in small volumes by local laboratories that served their local communities;
- were typically intended for use in diagnosing rare diseases or other uses to meet the needs of a local patient population or were generally similar to well-characterized, standard IVDs;
- tended to employ manual techniques (and did not use automation) and were performed by laboratory personnel with specialized expertise;
- were to be used and interpreted by physicians or pathologists in a single institution responsible for the patient (and who were actively involved in patient care); and
- tended to be manufactured using components legally marketed for clinical use, such as general purpose reagents or immunohistochemical stains marketed in compliance with FDA requirements.

This enforcement discretion approach for LDTs developed as a matter of general practice.

However, since 1976, the development and usage of LDTs have evolved considerably. LDTs are now more complex, sometimes including proprietary algorithms. Today's LDTs are also used more widely, by a more diverse population, with an increasing reliance on high-tech instrumentation and software, and more frequently for the purpose of guiding critical healthcare decisions. They are often performed in large volumes in reference laboratories for patients from

different institutions around the world and are sometimes assembled using components intended for research use only. Some LDTs are manufactured by corporations that market the IVDs nationwide as they accept specimens from patients across the country and run their tests in very large volumes in a single laboratory.[10] In this regard, most LDTs today are similar to other IVDs that have not been under FDA's general enforcement discretion approach.

Clinical laboratory tests are foundational to healthcare. The Centers for Disease Control and Prevention (CDC) estimates that 70 percent of medical decisions are based on laboratory test results (Ref. [16]). IVDs offered as LDTs are a growing sector of that market (Ref. [17]). Given the role these tests play in modern healthcare, their safety and effectiveness significantly impact public health. Although many of the IVDs offered as LDTs today are similar to other IVDs and may often serve the same role in clinical practice, FDA has generally not enforced applicable device requirements for LDTs. As a result, there is generally less assurance of the safety and effectiveness of IVDs offered as LDTs compared to other IVDs.

B. Need for the Rule

As the growing number of IVDs offered as LDTs entering and currently on the market (some of which may be problematic IVDs) typically are not reviewed by FDA, patients might be at risk when their providers rely on certain IVDs offered as LDTs to guide their care. Results from problematic IVDs can lead to delayed diagnosis or treatment of the true disease or condition, unwarranted interventions (some of which may carry risk of serious side effects), needless distress, progression of disease (in some cases costing the opportunity for life-saving treatment), and the spread of infectious diseases.

[10] See, e.g., Pew Research Center (Ref. [27]), Grand View Research (Ref. [17]), and Congressional Research Service (Ref. [73]). These observations are also informed by FDA's own experience, including the review of submissions and site visits, and staff with prior experience in the laboratory industry developing and running LDTs.

While laboratories that offer IVDs are regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA),[11] CLIA addresses laboratory operations and personnel qualifications and not the development of individual tests in a laboratory (see 42 U.S.C. 263a and 42 CFR part 493) (Ref. [18]). In particular, under CLIA, CMS does not:

- regulate laboratory test development;
- evaluate the performance of an IVD before the test is offered to patients and healthcare providers;
- 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);
- regulate certain manufacturing activities, such as design controls and acceptance activities;
- provide human subject protections for patients who participate in IVD clinical research trials; or
- require adverse event reporting.

By contrast, the device provisions of the FD&C Act and FDA's regulations focus on the safety and effectiveness of the IVDs themselves. Given this distinction, CMS has described the FDA and CMS "regulatory schemes" as "different in focus, scope and purpose, but […] intended to be complementary (Ref. [19])."

[11] Three federal agencies are responsible for administering the CLIA program: the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). Each agency has a unique role. FDA's role is limited to categorizing the complexity of tests, generally following FDA clearance or approval, whereas CMS generally is responsible for oversight of clinical laboratories. Additional information is available on FDA's website at: https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia.

FDA's experience with emergency use authorization (EUA) requests from laboratories for COVID-19 tests during the COVID-19 pandemic increased FDA's concerns about the safety and effectiveness of IVDs offered as LDTs.[12] While FDA had received requests for EUAs for tests from laboratories in prior emergencies, the scope of the COVID-19 pandemic resulted in an unusually high number of EUA requests from laboratories, revealing the approach that many laboratories might take to test validation. In an analysis of the first 125 EUA requests received from laboratories during the COVID-19 pandemic for molecular diagnostic tests, FDA found that 82 tests had design or validation problems, or both. The tests involved relatively well-understood techniques and the laboratories represented these tests as appropriately validated.[13] To the extent that this sample represents larger trends in the performance of IVDs offered as LDTs, it indicates the need for greater oversight.

Problems with IVDs offered as LDTs have also come to light in the scientific literature, news articles, and anecdotal reports submitted to the Agency, among other sources. Multiple publications in the scientific literature have described a high degree of variability among IVDs offered as LDTs (Ref. [20]). For example, in one study, analytical accuracy was significantly lower than that of the parallel test approved by FDA for almost half of the tests studied (Ref. [21]).

[12] These requests resulted in review because FDA did not generally exercise enforcement discretion for LDTs intended for emergencies/potential emergencies/material threats declared under section 564 of the FD&C Act.
[13] Memorandum to File from Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, RE: Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2 (September 22, 2023), available in Docket No. FDA-2023-N-2177

News and other outlets have also reported on problems with IVDs offered as LDTs, including the New York Times (Ref. [15]), and lawsuits have been filed relating to pharmacogenomic and non-invasive prenatal screening IVDs offered as LDTs.[14]

FDA has received complaints, allegations, and reports regarding IVDs offered as LDTs for oncology, non-invasive prenatal screening, and infectious diseases, among others. Some laboratories have submitted data to FDA in premarket submissions for their IVDs offered as LDTs, and we have observed that many failed to perform the appropriate studies to show that their IVDs work. Some have submitted data from appropriate studies, but the data show that their IVDs do not work. In both cases, laboratories have continued to offer such IVDs for clinical use.

While it is theoretically possible that, over time, patients and providers might learn the differences between competing tests and eventually stop purchasing ineffective tests regardless of regulation, that has not universally happened to date, even though the disparity between IVDs offered as LDTs and IVDs meeting applicable FDA requirements has been ongoing for decades. Further, we know from experience that providers and patients often do not even know what test was performed by a laboratory and, without widespread awareness of the different types of tests and regulatory disparities, we expect that learning of this kind would be rare, if it ever occurred, and would be complicated by the rapidly changing market, with new tests introduced regularly. Moreover, during the time that it would take for any such learning to occur, providers and patients may be using inaccurate or unreliable tests, with all the associated risks to patients. As for patients, ability to internalize the relevant risks may be precluded by not knowing the

[14] See Complaint, *In re Myriad Genetics, Inc. Sec. Litig*., No. 2:19-cv-00707-DBB (D. Utah 2019); Complaint, *Hickok* v. *Capone*, No. 2021-0686 (Del. Ch. 2021); Complaint, *Davis* v. *Natera, Inc*., No. 3:22 –cv-00985 (N.D. Cal. 2022); Complaint, *Carroll* v. *Myriad Genetics Inc.*, No. 4:22-CV-00739 (N.D. Cal. 2022); *Biesterfeld* v. *Ariosa Diagnostics, Inc.*, No. 1:21--CV-03085, 2022 WL 972281 (N.D. Ill. 2022); and Complaint, *Kogus* v. *Capone*, No. 2022-0047-SG (Del. Ch. 2022).

difference between IVDs offered as LDTs and FDA-authorized IVDs or having meaningful informed choice in the purchase decision.

Furthermore, FDA is aware that some entities have adopted business practices that claim a connection to laboratories in order to offer IVDs as LDTs, even when they are not LDTs, because they are not actually designed, manufactured, and used within a single laboratory (See for example Refs. [22] and [23]). For example, FDA notes:

- manufacturers offering unauthorized home specimen collection kits manufactured outside of the laboratory for use with LDTs;
- software developers offering software for high-risk clinical use with LDTs through laboratory partnerships;
- laboratories offering test kits previously alleged to be "research use only" test kits;
- manufacturers of home specimen collection kits with consumer facing platforms providing the ordering and resulting interface while outsourcing testing to unspecified laboratories; and
- contract manufacturers claiming to be consulting firms that design and validate tests for customer laboratories to perform.

This puts non-laboratory, conventional test manufacturers who develop IVDs, whose IVDs have not been under FDA's general enforcement discretion approach for LDTs, at a competitive disadvantage compared to laboratory manufacturers of IVDs offered as LDTs. IVD manufacturers who are not laboratories might currently be discouraged from investing time and resources into developing novel tests due to the concern that once the manufacturer receives marketing authorization for its test, laboratories will develop similar tests and market their tests

without complying with FDA requirements (Refs. [24] and [25]). We anticipate that applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs, and phasing out the general enforcement discretion approach for LDTs, will better assure the safety and effectiveness of IVDs offered as LDTs, and remove a disincentive for non-laboratory manufacturers to develop novel tests, thereby spurring innovation and access to IVDs for which there is a reasonable assurance of safety and effectiveness. Without the phaseout policy, and without better assurance of the safety and effectiveness of IVDs offered as LDTs, limited investment and healthcare funding may be expended on improving problematic IVDs.

The enforcement discretion approach for LDTs has created distortions in the diagnostics market.[15] These distortions not only complicate understanding the IVDs used in clinical practice, impeding FDA's ability to ensure the safety and effectiveness of IVDs, but might also disincentivize high standards of quality control and accuracy and thus entail social costs.[16]

In order to curtail offering of problematic tests, FDA is phasing out the general enforcement discretion for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs.

In addition, to ensure clarity and understanding by industry and the public, FDA is amending its regulations to make explicit that IVDs are devices under the FD&C Act including when the manufacturer of the IVD is a laboratory.

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[15] Market distortions may be associated with events, decisions, or interventions taken by governments, companies, or other agents that influence the market in ways that undermine optimal allocation as modeled under the First Fundamental Theorem of Welfare Economics. Related concepts include market failure, government failure or behavioral bias (Ref. [71]).

[16] Social costs are costs incurred from the viewpoint of society (including external costs), beyond just stakeholders (private costs). When laboratories avoid paying for external costs arising from their actions (such as costs to manufacture tests with a reasonable assurance of safety and effectiveness, and if borne by individuals not involved in the decision to order such tests—for example, taxpayers funding government health insurance), the costs to society as a whole (such as non-internalized worsened health outcomes from inaccurate test results) remain. External costs, along with private costs, affect whether society is operating at a socially efficient rate of output (Ref. [72]).

C. Purpose of the Rule

The purpose of the rule, which amends 21 CFR part 809, is to make explicit that IVDs are devices under section 201(h)(1) of the FD&C Act (21 U.S.C. 321(h)(1)) including when the manufacturer of the IVD is a laboratory. This amendment will reflect the fact that the device definition in the FD&C Act does not differentiate between entities manufacturing the device, and will provide further clarity to stakeholders affected by the accompanying changes to FDA's general enforcement discretion approach for LDTs.

In addition, as discussed in section V of the preamble to the rule, FDA is also phasing out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs (i.e., FDA's expectations for compliance will generally be the same). This phaseout policy includes limited enforcement discretion policies for specific categories of IVDs manufactured by a laboratory, including currently marketed IVDs offered as LDTs and LDTs for unmet needs. This phaseout policy is intended to better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs, while also accounting for other important public health considerations such as patient access and reliance. In addition, by applying the same general oversight approach to laboratories and non-laboratories that manufacture IVDs, FDA will give stakeholders more stability, clarity, and confidence, and facilitate investment in the development of innovative IVDs.

For additional discussion, see section III.B of the preamble.

D. Baseline Conditions

We consider the current environment, including the general enforcement discretion approach, as a reasonable approximation of the baseline (the projected future without phasing out

FDA's general enforcement discretion approach for LDTs) against which to measure the costs and benefits of the phaseout policy and the regulatory alternatives discussed in section II.J.

FDA has generally described LDTs as IVDs that are designed, manufactured, and used in a single laboratory that is certified under CLIA and that meets the regulatory requirements under CLIA to perform high complexity testing (Ref. [26]).[17] However, as discussed in the preamble and section II.F "Costs," the phaseout policy will affect not only LDTs, but IVDs manufactured and offered as LDTs, even if those IVDs do not fall within FDA's traditional understanding of an LDT because they are not designed, manufactured, and used within a single laboratory.[18, 19] Throughout this document, we refer to these IVDs as "IVDs offered as LDTs."

As described in section V of the preamble, FDA is including various enforcement discretion policies with regard to all applicable requirements for certain categories of tests manufactured by laboratories. One such category of tests is referred to in this document as "1976-Type LDTs." Such tests have the following characteristics common among LDTs offered in 1976 (discussed in section III of the preamble):

- use of manual techniques (without automation) performed by laboratory personnel with specialized expertise;
- use of components legally marketed for clinical use; and

[17] This includes laboratories operating under State licensure programs deemed exempt from CLIA.
[18] This discussion concerns only laboratories that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing (including laboratories operating under State licensure programs deemed exempt from CLIA), as other laboratories would be out of compliance with CLIA regulations if they were developing and performing tests that are not FDA-authorized. As noted in the preamble to the final rule, tests offered by such laboratories have never fallen within FDA's general enforcement discretion approach.
[19] According to its website, CMS regulates all laboratory testing (except research) performed on humans in the U.S. through CLIA. In total, CLIA covers approximately 320,000 laboratories, but we do not know how many of these laboratories meet the regulatory requirements under CLIA to perform high complexity testing. It is worth noting that the number of CLIA certified laboratories, including laboratories that meet the requirements under CLIA for high complexity testing, can vary over time as new laboratories acquire certifications and others may close or lose their certification (Ref. [18]).

- design, manufacture, and use within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing.

FDA will also continue the general enforcement discretion approach for Human Leukocyte Antigen (HLA) tests that are designed, manufactured and used in a single CLIA-certified, high-complexity histocompatibility laboratory that meets the requirements to perform high-complexity histocompatibility testing when used:

- in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing,
- for HLA antibody screening and monitoring, or
- for conducting real and "virtual" HLA crossmatch tests.

FDA will also continue the general enforcement discretion approach for tests intended solely for forensic (law enforcement) purposes. This approach has been in place for over 20 years and applies to such tests regardless of whether they are offered as an LDT.

FDA also intends to continue the general enforcement discretion approach for LDTs manufactured and performed within DoD or VHA. To meet the needs of their patient populations (i.e., military personnel, veterans, and their families) and fulfill their mandates, DoD and VHA often manufacture unique LDTs, such as tests for diseases or chemicals to which their patients may be exposed while serving abroad but which do not exist at home.

We lack information to quantify the number of tests that fall in the above categories and thus the exclusions are not assessed in this regulatory impact analysis.

FDA also intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements, with the exception of requirements under 21 CFR 820, subpart M (Records), for currently marketed IVDs offered as LDTs that were first marketed prior to the

date of issuance of this rule that are not modified, or that are modified in certain limited ways. FDA generally expects compliance with premarket review and QS requirements when a laboratory changes the indications for use of the IVD, alters the operating principle of the IVD (e.g., changes in critical reaction components), includes significantly different technology (e.g., addition of artificial intelligence / machine learning to the test algorithm, a change from targeted sequencing to whole genome sequencing, a change from immunoassay to mass spectrometry, or a change from manual to automated procedures), or adversely changes the performance or safety specifications of the IVD.

In addition, FDA intends to exercise enforcement discretion and generally not enforce premarket review and QS requirements, with the exception of requirements under 21 CFR 820, subpart M (Records), for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. For the purpose of this phaseout policy, FDA considers an LDT to be for an unmet need where there is no available FDA-authorized test that meets the patient's needs. This may be because – (1) there is no FDA-authorized IVD for the disease/condition; (2) there is an FDA-authorized IVD for the disease/condition but it is not indicated for use on the patient, or a unique attribute needs to be added to the IVD to meet the patient's needs; or (3) there is an FDA-authorized IVD but it is not available to the patient. This is discussed further in section V.B.3 of the preamble.

FDA also intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs approved by NYS CLEP.

We expect that a number of laboratories offering IVDs as LDTs, and those IVDs, do not currently meet applicable requirements—including premarket review, quality system,

registration and listing, and adverse event reporting requirements—given FDA's general enforcement discretion approach for LDTs.

We do not have complete information about IVD performance or patient harm. As discussed in detail in section III.B of the preamble, FDA has increasingly seen problems with IVDs offered as LDTs that have caused or might be causing harm. However, the tests involved likely do not represent all problematic tests that might be affected by the phaseout of the general enforcement discretion approach for LDTs, as laboratories do not typically submit premarket submissions for IVDs offered as LDTs to FDA or report adverse events associated with those tests given the general enforcement discretion approach.

Without registration and listing information, it is difficult to estimate the exact baseline number of manufacturers of IVDs offered as LDTs that will be affected by the phaseout policy. It is also difficult to estimate the number of IVDs offered as LDTs currently on the market, when or why many of them are used, or exactly how they each perform compared to other IVDs.

Without adverse event reporting or other information that FDA will obtain upon the phaseout of the general enforcement discretion approach, it is difficult to estimate the exact baseline number of patients that can benefit from the phaseout of the general enforcement discretion approach given current information. In order to account for potential uncertainty and variability, we present all expected costs and benefits in ranges of low, central, and high estimates. We address baseline risks (and costs due to risks) in the benefits section of this analysis.

1. Number of Affected Entities

Since laboratories that offer IVDs as LDTs have not generally registered and listed, we do not know the exact number of laboratories or IVDs offered as LDTs that will be affected by the phaseout of the general enforcement discretion approach for LDTs.

Comments suggested we use CMS data to estimate the number of affected labs. Using the CMS data, we estimate that there are 11,808 high complexity CLIA laboratories that have IVDs offered as LDTs that will be affected by the phaseout of the general enforcement discretion approach. We therefore revise our original estimate of 12,000 to 11,808. The steps in developing this estimate are explained in appendix A. Laboratories that meet the requirements to perform high complexity testing are the only laboratories that can perform LDTs under CLIA regulations, because LDTs are considered high complexity tests (Ref. [27]). Additionally, while CLIA regulations contemplate that such laboratories may deploy IVDs offered as LDTs, we do not expect that every such laboratory does so. We are not aware of suitable sources for the exact number of such laboratories that are currently offering IVDs as LDTs.

We rely on information about laboratories and IVDs in NYS to estimate the percent of high complexity labs that make IVDs offered as LDTs (Ref. [28]). NYS requires laboratories offering tests to NYS residents, whether or not the laboratory is located in NYS, to obtain a permit through the NYS CLEP, as well as "explicit test-specific approval" for certain IVDs that are not "designated as FDA-cleared, approved or exempt." (Ref. [29]) To FDA's knowledge, NYS is the only state that requires approval for LDTs that are not FDA-cleared, approved, or exempt. Further, NYS is a relatively large space with a variety of demographics, including urban to rural areas, and a variety of laboratories such as academic medical centers, reference laboratories, public health laboratories, and local hospital laboratories, similar to the variety found throughout the U.S. Therefore, FDA determined that the information about laboratories

and IVDs in NYS could be extrapolated to estimate the number of laboratories throughout the U.S. that might be offering IVDs as LDTs.

NYSDOH provided information indicating that there are approximately 500 laboratories located in NYS with a NYS CLEP permit that are certified under CLIA and that meet or exceed the regulatory requirements under CLIA to perform high complexity testing, and that approximately 50 of such laboratories offers at least one IVD as an LDT approved by NYS CLEP (Ref. [28]). From these data, we calculate that approximately 10% of laboratories located in NYS that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing are manufacturing IVDs offered as LDTs.

For our primary estimate, we assume that NYS is representative of the U.S. laboratory community, as discussed above. Based on the information from NYS and the assumption that NYS is representative of the entire U.S., we estimate that approximately 10% of 11,808 (or 1,181) laboratories in the U.S. that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing currently manufacture IVDs offered as LDTs. To account for potential variability across the country, we estimate the proportion of high complexity laboratories making IVDs offered as LDTs to vary from 5% of 11,808 (or 590) laboratories to a high estimate of 20% of 11,808 (or 2,362) affected laboratories by reducing the primary estimate by 50% and doubling the primary estimate, respectively.

Based on these two sources and methods, for purposes of this analysis, we use 590, 1,181 and 2,362 as low, central (primary), and high estimates of the number of laboratories affected by the phaseout of the general enforcement discretion approach for LDTs. We also expect that there will be new laboratories entering the market every year. To calculate the number of new laboratories per year, we use an average of firms' entry and exit rates from 2010 to 2018 in the

United States (approximately 8 percent) (Ref. [30]). Multiplying this by the number of affected entities, we estimate the number of new laboratories per year to range from 47 to 189, with a primary estimate of 94.[20]

Because there is no single source containing information on the number of IVDs offered as LDTs currently on the market, FDA also used information about laboratories and IVDs reviewed in NYS to extrapolate estimates for affected IVDs across the country. According to NYSDOH's website, there are currently approximately 2,200 IVDs with approval from NYSDOH offered by laboratories located in NYS (Ref. [29]). NYSDOH provided the number of distinct laboratories within NYS that are certified under CLIA, that meet the regulatory requirements under CLIA to perform high complexity testing, and that are manufacturing and offering at least one IVD offered as an LDT (Ref. [28]), as well as the breakdown of risk categories for submissions to NYS, as determined by NYS CLEP risk criteria. From these data, FDA calculated that each laboratory in NYS that manufactures IVDs offers an average of 67 IVDs as LDTs. Extrapolating to the rest of the country, FDA estimates that 39,557, 79,114, or 158,227 IVDs may be currently offered as LDTs and therefore affected by the phaseout of the general enforcement discretion approach, based on the low, central, and high estimates of affected entities discussed above (see Table 2). These estimates assume that NYS is representative of the U.S. laboratory community.

We took a similar approach to estimating the number of new IVDs offered as LDTs that are expected to be introduced per laboratory per year. NYSDOH provided information indicating

[20] We also examined census data. According to 2017 Statistics of U.S. Businesses (SUSB) data from the U.S. Census there are 3,365 Medical Laboratories (represented by NAICS code 621511). While data from the Census does not provide information on the number of laboratories under NAICS code 621511 that specifically manufacture IVDs offered as LDTs, if we assumed half of the entities were IVD manufacturers and the other half were laboratories, we would get 1,683 laboratories. The difference between this estimate and our primary estimate (502=1,683-1,181) is less than 5% of our primary estimate. We also consider varying our estimates by -5% and +10% to be sufficient for estimating the range of variability between our low and high estimate.

that laboratories within NYS that manufacture IVDs offered as LDTs introduce an average of 6 new IVDs offered as LDTs per year.[21] For purposes of this analysis, we assume that laboratories in NYS are representative of the U.S. laboratory community, and estimate that 3,542, 7,085, or 14,170 new IVDs offered as LDTs may be affected per year. We also expect that there would be new IVDs offered as LDTs from new laboratories entering the market every year.[22] In addition, we expect 50 percent of currently marketed IVDs offered as LDTs (34 IVDs offered as LDTs per laboratory = 67 * 0.5) will be modified in such a way as to require premarket review over the next twenty years. We thus estimate 2 IVDs offered as LDTs per year per laboratory will be modified in such a way as to require premarket review (2 = 34 / 20 years). The total number of new IVDs offered as LDTs per year is estimated to range from 5,007 to 20,026, with a primary estimate of 10,013. We understand anecdotally that some large reference laboratories may make as many as 100 new IVDs per year, whereas smaller or more specialized laboratories may focus on one or a few IVDs overall and may not introduce many or any new IVDs every year. Throughout this analysis, we define the terms "affected labs" and/or "affected entities" as laboratories offering IVDs as LDTs and therefore affected by the phaseout of the general enforcement discretion approach for LDTs. In a similar manner, we also define the terms "affected IVDs" as IVDs offered as LDTs associated with costs as incurred during their relevant policy stages 1 through 5 (discussed in detail in section II.F).

[21] NYSDOH provided information indicating that, on an annual basis, NYS approves approximately 200 IVDs offered as LDTs across approximately 50 laboratories within NYS, or approximately 4 IVDs offered as LDTs per NYS lab per year. Although they receive test packages for them, NYS does not approve low-risk tests. Based on NYSDOH's accounting of test packages submitted to NYSDOH's CLEP program, we estimate that approximately 34% of the IVDs being offered as LDTs by NYS labs are tests that NYSDOH considers to be low-risk. To account for all tests, including low-risk tests, and assuming that NYS is an appropriate proxy for the rest of the U.S., FDA used an estimate of 6 new IVDs offered as LDTs per laboratory per year.

[22] We use an average of firms' entry and exit rates from 2010 to 2018 in the U.S. (8 percent) (Ref. [30]).

Table 2 shows the estimated number of laboratories and IVDs offered as LDTs affected by the phaseout of the general enforcement discretion approach for LDTs.

Table 2. Estimated Number of Laboratories and IVDs Offered as LDTs Affected by this Rule

	Primary Estimate	**Low Estimate**	**High Estimate**
Affected Labs	1,181	590	2,362
New Affected Labs Entering the Market Per Year	94	47	189
Affected Tests Currently on the Market	79,114	39,557	158,227
New Affected Tests Per Year	10,013	5,007	20,026

Notes: Product across table may not be exact due to rounding. The number of new affected IVDs per year include currently marketed IVDs that would be modified and new affected IVDs from both affected labs and new labs entering the market per year. These numbers reflect the baseline numbers for affected laboratories and affected tests and are further adjusted in later sections of this analysis to estimate costs under Stages 4 and 5, where only a subset of these laboratories and tests may incur costs, as described in sections II.F.4 and II.G.

2. Baseline Market Revenue

Data from the 2017 U.S. Census for the entire industry under NAICS code 621511 reported 3,365 firms with $36 billion in annual revenues.[23] From Table 2 above, we estimate 1,181 affected laboratories or firms which represent 35% of the 3,365 firms in the Census data. If we assume the same average annual receipts for all firms, then the corresponding annual receipts for affected laboratories would represent 35% of total annual receipts or $15 billion (in 2022 dollars).[24]

[23] Medical laboratories under NAICS 621511. are a subset of NAICS 621500 which is described as medical and diagnostic laboratories and also includes NAICS 621512 for Diagnostic imaging centers. For purposes of this analysis, we only use revenue data associated with NAICS 621511which includes revenue for both IVDs offered as LDTs and other IVDs (although the Census does not distinguish between IVDs offered as LDTs and other IVDs). Source: https://www.census.gov/data/tables/2017/econ/susb/2017-susb-annual.html

[24] We convert 2017 dollars to 2022 dollars using CPI of 1.19 for 2017-2022. The product of $36 billion x 0.35 x 1.19 is about $15 billion.

In Table 3, we estimate annual industry revenue in 2023 between $19 and $21 billion based on a projection from 2017 Census data of the $15 billion using compounded annual growth rates (CAGRs) of 4.2% and 6% (Refs. [17] [31]).[25]

Table 3. Estimated Market Revenue for IVDs Offered as LDTs ($1,000, 2022 U.S. dollars)

Year	**Primary** (Average between low and high projection)	**Low** Projection ($1,000) (4.2% CAGR)	**High** Projection ($1,000) (6% CAGR)
2023	$20,093,935	$19,062,398	$21,125,471
2030	$28,594,674	$25,424,450	$31,764,898

3. Baseline FDA Premarket Reviews of Submissions/Applications

To better understand the magnitude of anticipated premarket submissions/applications for IVDs offered as LDTs that FDA would receive on an annual basis, Table 4 below shows the 5 year average number of submissions/applications for all devices (2017-2021) along with the estimated annual number of submissions/applications expected for IVDs offered as LDTs after this rule become effective (Ref. [32]).[26] The estimated annual reviews for premarket submissions/applications are adjusted to account for the enforcement discretion polices discussed

[25] The calculation for future value in 6 years using a CAGR of 4.2% is:
Future Value (FV) = Present Value (PV) x (1+4.2%)^6 = $15 billion x (104.2%)^6 = $19 billion.

[26] For the purposes of this document, we used PMAs, 510(k)s, and De Novos as the primary submission types anticipated for IVDs offered as LDTs. We assume that some IVDs offered as LDTs may also be biological products subject to licensure under section 351 of the Public Health Service Act and instead require submission of a Biologics License Application (BLA). Most licensed IVDs are tests intended for use as blood donor screening tests or HCT/P donor screening tests subject to 21 CFR 610.40 and 1271.80(c), respectively, or tests for determination of blood group and Rh factors subject to 21 CFR 640.5. As explained in the preamble, FDA's general enforcement discretion approach for LDTs has never applied to such tests. Therefore, we anticipate that there will be a limited number of IVDs offered as LDTs that are subject to licensure. While it is possible that some IVDs offered as LDTs may be submitted for review in Humanitarian Device Exemption (HDE) applications, the number of HDEs for IVDs has historically been negligible and many LDTs eligible for review under an HDE application may also fall within the enforcement discretion policy for certain LDTs for unmet needs. The volume of such submissions, if any, is expected to be much lower than the volume of PMAs, 510(k)s, and De Novos and, as discussed in the preamble to the rule, laboratories that intend to submit a BLA or HDE application for an IVD offered as an LDT should do so within the same timeframe for submission of PMAs under the phaseout policy. For the purposes of this document, we assume BLAs to be equivalent to PMAs in costs and benefits, and we assume HDEs to have a negligible impact on the calculations in this document. Therefore, the portion of IVDs offered as LDTs that are expected to submit BLAs and HDEs are included in the PMA numbers.

above, potential reclassifications of class III IVDs to class II, and the 510(k) Third Party Review Program.

Table 4. FDA Review Workload by Submission Type

Submission/Application Type	5-Year Average (FY 2017 to 2021)	Expected Annual Reviews for New IVDs Offered as LDTs		
		Primary	Low	High
Original PMAs, PDPs, Panel-Track PMA Supplements	73	103*	52*	206*
510(k) Premarket Notifications	3,877	1,090	545	2,179
De Novo Classification Requests	66	267	134	534

Note: FDA annual reviews of Q-submissions, MDRs and IDE applications are not included in Table 4 but are estimated in section II.G Budgetary Impacts and described in Table 38.
* The estimated reviews include original PMAs and panel-track PMA supplements. See Table 29 and Table 31 for estimated numbers of original PMAs and panel-track PMA supplements, respectively. Totals may not add due to rounding.

4. Baseline Risk of Problematic IVDs

We measure benefits of phasing out the general enforcement discretion approach for LDTs against a baseline scenario in which FDA continues the general enforcement discretion approach with respect to all applicable requirements for all IVDs offered as LDTs. Due to the current general enforcement discretion approach for LDTs, we lack systematic data on the exact incidence of harms specifically resulting from usage of problematic IVDs offered as LDTs that can be avoided by phasing out the general enforcement discretion approach for LDTs.

To estimate the baseline incidence of harms that can be avoided by phasing out the general enforcement discretion approach for LDTs, we focus mainly on three broad disease categories identified by Newman-Toker et al. (2021) as accounting for about 75% of serious misdiagnosis-related harms in the U.S.: cancers, cardiovascular disease, and infections (Ref. [33]). As described in the following section, we multiply the numbers of U.S. patients in each disease category—estimated from sources described below—by rates from literature of the

proportions of patients in each category that are tested using IVDs. Based on Rychert et al. (2023) (Ref. [2]), as described in section II.E.1, we estimate that 3.9% to 45% of patients tested with IVDs are tested with IVDs offered as LDTs. This yields our baseline estimates of the numbers of patients tested using IVDs offered as LDTs. To estimate usage specifically of problematic IVDs that can be curtailed by phasing out the general enforcement discretion approach for LDTs, we refer to statistics from NYS CLEP on application review outcomes and FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests. Since we do not expect that LDTs approved by NYS CLEP would undergo FDA premarket review, when estimating numbers of U.S. patients in each disease category, we exclude from this analysis the number that we attribute, proportionally by population, to New York state. We note however for LDTs approved by NYS CLEP, FDA intends to exercise enforcement discretion with respect to premarket review requirements but not other applicable requirements under the FD&C Act and FDA regulations.

Lacking systematic data on the exact issues with applications for LDTs initially rejected by NYS CLEP and those LDTs' roles in the process of diagnosis, we consider a range of rates at which avoidable errors might result from usage of problematic IVDs offered as LDTs.

Finally, in section II.E.3 "Summary of Benefits," we adjust estimated total benefits to account for the enforcement discretion policy for IVDs offered as LDTs that are already currently on the market. As a result of exercising enforcement discretion with respect to premarket review and QS requirements, with the exception of requirements under 21 CFR 820 subpart M (Records), for currently-marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule, IVDs offered as LDTs will generally undergo premarket review only in certain circumstances. However, FDA expects these IVDs to be in

compliance with other applicable requirements under the FD&C Act and FDA regulations, including post market requirements, as discussed in the phaseout policy. In order to account for this, we adjust estimated total benefits in each year—beginning with enforcement of QS and premarket review requirements—based on the proportions of IVDs falling within an enforcement discretion policy versus IVDs not falling within an enforcement discretion policy. We note, however, as described in section V.B.3 of the preamble, FDA intends to take targeted steps to address currently marketed IVDs offered as LDTs that are problematic. In particular, we intend to use available tools to identify and act against currently marketed IVDs offered as LDTs that specifically raise concerns, such as IVDs that are potentially inaccurate or poorly validated.

E. Benefits

Expected benefits of phasing out the general enforcement discretion approach for LDTs consist mainly of avoided harms to patients, including unnecessary costs, monetary and otherwise, that would result from usage of problematic IVDs offered as LDTs. Harms can vary in severity according to the particular problematic aspects of an IVD and their consequences for patient care.

We expect the phaseout to produce both health and pecuniary benefits via averting diagnostic error and its consequences, such as incorrect or unnecessary treatment, treatment delays, and disease progression or transmission. Pecuniary benefits also include reduced spending on problematic IVDs offered as LDTs, including non-invasive prenatal screening (NIPS) tests, as well as reduced spending on litigation over alleged harms caused by problematic IVDs.

1. Reduction in Harms from Diagnostic Errors

We expect public health benefits from phasing out the general enforcement discretion approach for LDTs due to improved safety and effectiveness of IVDs offered as LDTs. To

estimate the baseline incidence of harms that can be avoided by the phaseout, we focus mainly on three broad disease categories identified by Newman-Toker et al. (2021) as accounting for about 75% of serious misdiagnosis-related harms in the U.S.: cancers, cardiovascular disease, and infections (Ref. [33]).

a. Cancer: Mortality Risk

We quantify health benefits in the form of reduced baseline mortality risk based on expected reduction of cancer related misdiagnosis with problematic IVDs offered as LDTs. Based on the data available to us, this analysis focuses specifically on benefits in the form of reduced mortality risk (i.e., benefits associated with reducing false negative diagnoses). However, we anticipate that the phaseout policy will lead to other benefits as well, such as reduced risk of undergoing unnecessary, potentially harmful treatments based on false positive diagnoses.

We also present these estimates with the caveat that the incidence of misdiagnosis-related mortality depends on the manner of attribution of harm to diagnostic delays, and therefore our estimates might imply a number of cases bearing mortality risk consequences that differs from certain available estimates of the number of deaths attributable to misdiagnosis (Ref. [34]).[27] With a correct diagnosis, death can be delayed to a later date than one following an incorrect diagnosis. However, depending on when a misdiagnosis occurs, death might still be delayed to a degree depending on how soon a patient seeks follow-up and receives a correct diagnosis at a later time. Life expectancy in this case would still be shortened compared to if the initial

[27] From Newman-Toker (2023), annual US incidence was 6.0 M vascular events, 6.2 M infections and 1.5 M cancers. Per 'Big Three' dangerous disease case, weighted mean error and serious harm rates were 11.1% and 4.4%, respectively. Extrapolating to all diseases (including non-'Big Three' dangerous disease categories), the authors estimated 795,000 total serious harms annually in the USA (plausible range 598 000–1 023 000). Sensitivity analyses using other assumptions estimated 549 000 serious harms. Results were compatible with setting-specific serious harm estimates from inpatient, emergency department and ambulatory care (Ref. [34]).

diagnosis had been correct, but this would not necessarily be counted as a death due to misdiagnosis.[28] It is also possible that the differences in risk of death from a delayed diagnosis could be attributable to treatment differences such as fewer effective therapies for later-stage lung cancers contributing to the adverse impact of diagnostic delays (Ref. [33]).

Although we do not estimate the benefits from avoiding false positives, accurate testing for patients can help maximize the benefits of certain therapies that patients need to treat or manage their condition. False test results may result in some treatments being denied to eligible patients, which may worsen their health outcomes.

Expected Reduction in Cancer Misdiagnosis

To estimate the reduction in cancer mortality risk from the phaseout policy, we start from an estimate of annual deaths attributable to diagnostic error and apply four probabilities: the probability of a patient having been tested with an IVD; the probability that the IVD had been offered as an LDT; the probability that the IVD offered as an LDT was problematic; and, finally, the probability that the problematic IVD offered as an LDT resulted in preventable diagnostic error. With respect to this last probability, we note that an IVD that yields a false result in an individual case is not necessarily a problematic IVD (indeed, no test is perfect 100% of the time).

Newman-Toker et al. 2019 (Ref. [35]) state that about 5-10% of the 2.7 million deaths annually in the United States are attributable to diagnostic error—or between 0.135 million and 0.27 million fatalities across all misdiagnosed conditions. Based on the annual US incidence of serious misdiagnosis-related harms across vascular events, infections, and cancers per Newman-Toker et al. 2023 (Ref. [34]), we estimate that about 11% (= 1.5M / 13.7M) of misdiagnosis-

[28] In general, the phaseout policy may reduce the risk of dying earlier or at a certain age (also referred to as the hazard function). This change in the hazard function can be expressed as a reduction in the expected number of deaths in a specified time period (less than one for an individual) or as an increase in the expected number of years lived (Ref. [74]).

related fatalities are associated with cancer. [29] This results in a range of 0.015 million, 0.022 million and 0.03 million misdiagnosis-related deaths from cancer.

Excluding the state of New York proportionally by population,[30] we assume that about 20,900 U.S. misdiagnosis-related cancer deaths occur outside of NY and could thus potentially involve tests not approved by NYS CLEP. It is likely that some patients outside of the state of New York are also tested with LDTs approved by NYS CLEP and hence would not necessarily benefit from the phaseout of enforcement discretion for premarket review requirements but will still benefit from the phaseout of enforcement discretion for other requirements, as would patients inside the state of New York. According to Rohr et al. (2016), 91% of U.S. oncology patients undergo IVD testing (Ref. [36]). Using test orders from a U.S. academic hospital system, Rychert et al. (2023) estimate that IVDs offered as LDTs are 3.9% of test order volume and 45% of distinct assays (Ref. [2]). In estimating the percent of patients tested with IVDs who are tested with IVDs offered as LDTs, we thus consider a range from 3.9% to 45%, with a primary estimate of 10%. Using the primary rate, we estimate that about 13,700 U.S. (non-NY) cancer patients would rely on IVDs offered as LDTs (= 150,554 x 0.91 x 0.10).

To estimate the number of these patients tested with IVDs offered as LDTs that would not be authorized by FDA following a premarket submission to the Agency (i.e., following the phaseout of the general enforcement discussion approach), we consult FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests and statistics from

[29] As noted above, per Newman-Toker et al. (2023), annual US incidence was 6.0 M vascular events, 6.2 M infections and 1.5 M cancers.

[30] According to the Census Bureau as of July 1, 2022, the population of NY was 19,677,151, and the population of the U.S. was 333,287,557. We thus assume that about 5.9% (= 19,677,151 / 333,287,557) of new U.S. cancers are in NY. For the population estimates used, refer to: https://www.census.gov/quickfacts/fact/table/US/PST045222.

NYS CLEP on application outcomes and assume that similar rates of initial denial would apply under FDA oversight.

A public comment from NYSDOH informed us that, since September 30, 2021, among applications subject to technical review:

- 46% were approved based on the original application;
- another 33% were approved in a second round of review after the applicant provided additional information; and
- 20% could not be approved after the second round of review (though they might have been approved later) (Ref. [12]).

Regarding applications not initially approved, NYSDOH stated in its comment:

> "Tests that are not approved based on the original application have a range of issues. Analytical validity issues include design flaws, inadequate validation data, and process problems that call into the question the reliability of the results. For example, the test may not be capable of detecting the target analytes. One application claimed to detect cytomegalovirus (CMV) in a transplant recipient population, but a primer/probe design flaw resulted in the detection of only two CMV subtypes. This error would have endangered patient safety and was only identified during NYS CLEP review. The laboratory redesigned the assay with input from NYS CLEP subject matter experts so that all four subtypes could be detected." (Ref. [12])

We thus consider a range of scenarios reflecting different possible rates of problematic IVDs offered as LDTs. As a low estimate, we consider that 22% of EUA requests in FDA's 2020 assessment of EUA requests from laboratories for molecular diagnostic COVID tests had

significant design issues and indications for use issues.[31] As a high estimate, we use the 54% of submissions that are not initially approved by New York State. We consider initial approval rates because information contained in New York State's public comment suggests that "additional information" included in response to original review may include design changes, and thus tests not initially approved might, without review, have gone on to yield unreliable results. For our primary estimate, we average the above two, resulting in 38%.

In the central scenario with an expected initial rejection rate of 38%, about 720 misdiagnosis-related cancer deaths involve patients tested using IVDs offered as LDTs that will not be authorized by FDA following a premarket submission—at least without changes. We assume that some of the time when these IVDs are used, they yield inaccurate results that would not occur using an IVD that could be authorized by FDA. Of these instances of inaccurate results, some might be caught during follow-up or other parts of the process of diagnosis before leading to harm from diagnostic error.

Lacking systematic data on the exact issues with applications for IVDs offered as LDTs initially rejected by NYS CLEP and these LDTs' roles in the process of diagnosis, we consider a range of rates at which avoidable error might result from usage of problematic IVDs offered as LDTs: from a low of 25% to a high of 75%, with a central estimate of 50%. However, some of these errors might not have consequences for patient care if a patient would in any case be unable or unwilling to obtain treatment. A patient diagnosed with cancer may go untreated for various reasons—including, in some cases, because no effective treatment exists. Ward et al. (2013) analyze data on nontreatment of cancer from the National Cancer Data Base and the Iowa

[31] Memorandum to File from Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, RE: Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2 (September 22, 2023), available in Docket No. FDA-2023-N-2177.

Cancer Registry, which show that between roughly 8 and 12 percent of newly diagnosed cancer patients in Iowa did not receive a first course of treatment (Ref. [37]). Assuming that Iowa cancer patients are representative of the rest of the U.S., we thus estimate that diagnostic error has treatment implications for 88% to 92% of patients, with a central estimate of 90%. Thus, using our central estimates, we expect the phaseout policy to avoid about 325 harms from diagnostic error among cancer patients.

Table 5. Avoidable Harms Related to Diagnostic Error Among Cancer Patients

	Primary	Low	High
a) Deaths from Misdiagnosis (Non-NYS)	20,863	13,908	27,817
b) Percent Tested with IVDs	91%	91%	91%
c) Probability of IVD Being Offered as an LDT	10.0%	3.9%	45.0%
d) Patients Tested with IVDs Offered as LDTs (= a * b *c)	1,898	494	11,391
e) Percent of IVDs offered as LDTs Not Authorized by FDA Following a Premarket Submission	38%	22%	54%
f) Tests Using Problematic IVDs Offered as LDTs (= d * e)	721	109	6,151
g) Percent Leading to Diagnostic Error	50%	25%	75%
h) Treatment-to-Diagnosis Ratio	0.9	0.88	0.92
i) Harms Avoidable by the Phaseout Policy (= f * g * h)	325	24	4,244

Value of Reduced Mortality Risk

As a first step in valuing reduced mortality risk from the phaseout policy, we estimate the gain in life expectancy associated with a correct diagnosis for someone who has cancer.

First, we consult 2023 data on estimated new cancer cases along with the five-year relative survival rate covering 2012-2018 (Ref. [38]). The five-year relative survival rate (RSR) in column B of Table 6, represents the percentage of individuals surviving their cancer diagnosis 5 years after diagnosis compared to individuals who are cancer free.[32] We then use the RSR to

[32] Relative survival is a net survival measure representing cancer survival in the absence of other causes of death. Relative survival is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the

estimate the absolute survival rate (of individuals with cancer who are diagnosed) further down below.

At the bottom of column D, we obtain the average five-year RSR across cancer sites, weighting by percent of total new cancer cases. For example, the weight on the RSR for breast cancer is the number of breast cancers divided by the sum of all new cancer cases (290,560 / 1,818,030 = 16%). The estimated five-year weighted average RSR for all new cancer cases is the sum of column D, 68.6%.

Table 6. Calculating the Weighted Average Relative Survival Rate (RSR) for New Cancer Cases

Site	Estimated New Cases (2022) A	Relative Survival (%) (2012–2018) B	% New Cases C	RSR x Percent weight D (=B*C/100)
Breast	290,560	90.5	16%	14.46
Prostate	268,490	96.8	15%	14.30
Lung and Bronchus	236,740	22.9	13%	2.98
Colon and Rectum	151,030	65.1	8%	5.41
Melanoma of the Skin	99,780	93.7	5%	5.14
Bladder	81,180	77.1	4%	3.44
Non-Hodgkin Lymphoma	80,470	73.8	4%	3.27
Kidney and Renal Pelvis	79,000	76.5	4%	3.32
Uterus	65,950	81.3	4%	2.95
Pancreas	62,210	11.5	3%	0.39
Leukemia	60,650	65.7	3%	2.19
Oral Cavity and Pharynx	54,000	68	3%	2.02
Thyroid	43,800	98.4	2%	2.37
Liver and Intrahepatic Bile Duct	41,260	20.8	2%	0.47
Myeloma	34,470	57.9	2%	1.10
Other	168,440	60.35	9%	4.78
Sum	**1,818,030**		100%	**68.60%**

Note: Product across table may not be exact due to rounding.

proportion of expected survivors in a comparable set of cancer free individuals. The formulation is based on the assumption of independent competing causes of death. The relative survival adjusts for the general survival of the U.S. population for that race, sex, age, and date at which the age was coded.

Thus, on average, a person with cancer who is diagnosed has 68.6% of the chance of living another five years than a person has who is cancer free. According to the National Cancer Institute, the median age of a cancer diagnosis is 66 years (Ref. [39]). Per CDC life tables, the 5-year survival rate for all age-66 individuals is approximately 91.13%.[33] To estimate the absolute 5-year survival of persons with cancer who receive a correct diagnosis from diagnostic testing, we multiply the RSR of 68.60% by 91.13%, thereby obtaining 62.52%. This estimate is likely lower than the true 5-year survival of persons with cancer who receive a correct diagnosis from diagnostic testing for the following reasons: 1) 91.13% does not in fact represent the 5-year survival rate of cancer-free individuals aged 66, but instead the 5-year survival rate of all age-66 individuals, including those with cancer, and 2) the SEER data attempts to represent all cases, which would thus include some that are missed upon initial diagnostic testing and only detected later. Based on the above, and the fact that the 5-year survival rate of 62.52% is more than half, or 50%, the median remaining life expectancy of someone with cancer who is correctly diagnosed by diagnostic testing is at least 5 years.

Next, based on survival of untreated individuals, we estimate the median remaining life expectancy of someone with cancer who is not diagnosed as such. The median survival time for untreated individuals is 2.3 years in cases of breast cancer (Ref. [40]) and 11.94 months, or 0.995 years, in cases of lung cancer (Ref. [41]). We average these two survival times, weighting by the numbers of new cases of breast and lung cancer, respectively, from Table 6 above, and thus obtain a survival time for untreated cancer patients of about 1.71 years. While we acknowledge that uncertainty is introduced by assuming that lung and breast cancers are representative of cancer in general, we received no comment indicating that this assumption is unsuitable.

[33] Calculated from Table 1 "Life table for the total population: United States, 2020" in the report "United States Life Tables, 2020," available at: https://www.cdc.gov/nchs/data/nvsr/nvsr71/nvsr71-01.pdf

We therefore estimate the gain in life expectancy from appropriate treatment upon diagnostic testing to be about 3.29 years (= 5 – 1.71). Thus, for an age-66 person with cancer who has just been tested, treating the cancer is worth about 3.29 more years of life starting about 1.71 years from the time of testing. Table 7 shows these life years discounted to the time of the diagnostic test at rates of three and seven percent.

Table 7. Life Years Due to Treatment of Cancer

Time from treatment (years)	Treatment	Discounted to time of treatment (3%)	Discounted to time of treatment (7%)
1.714	1	0.951	0.890
2.714	1	0.923	0.832
3.714	1	0.896	0.778
4.714	0.286	0.249	0.208
Total	3.286	3.018	2.708

We note that untreated and undiagnosed cancers may not have the same average prognosis. A patient diagnosed with cancer may go untreated for various reasons—including, in some cases, because no effective treatment exists.

Finally, we value these mortality risk reductions (at the time of the diagnostic test) using estimates of the value per statistical life year (VSLY), which is the rate at which a consumer or patient substitutes money for reductions in mortality risk, measured by the willingness to pay for an increase in life expectancy by one year. We use VSLYs derived from the value of a statistical life (VSL) under assumptions of three and seven percent discounting, paired with estimates of the statistical life years gained per case. [34,35] VSLYs are those projected for 2024 but using 2022 base year dollars for consistency with the rest of this analysis. Table 8 below represents our

[34] The approach for valuing mortality risk reductions is generally based on estimates of the value per statistical life (VSL), from which a value per statistical life year (VSLY) is derived. The VSLY values presented are updated to 2022 dollars per HHS guidance (Ref. [42]).
[35] We note that the HHS estimates of VSLY depend on the choice of discount rate.

estimates of the value (at the time of the diagnostic test), of the additional expected life years from an accurate diagnosis.

Table 8. Estimated Value Per Case of Accurate Diagnosis (2022$)

	(a) VSLY (3% discounting)	(b) Value Per Case (VSLY 3%) (= a * 3.018)	(c) VSLY (7% discounting)	(d) Value Per Case (VSLY 7%) (= c * 2.708)
Primary	$546,735	$1,650,181	$915,435	$2,479,329
Low	$255,143	$770,084	$427,203	$1,157,020
High	$832,253	$2,511,942	$1,393,495	$3,774,090

Note: Product across table may not be exact due to rounding.

To estimate total benefit in Table 9 below, we multiply the estimated reduction in harms by the benefit per avoided harm and by the portion of relevant risk not already internalized in decision-making by medical providers and patients. Because providers who frequently order tests might note quality trends across different labs, we assume that only 95% of the risk of problematic IVDs offered as LDTs is not already internalized at baseline, with a range from 90-100%. Total internalization is unlikely, because without deliberate study of records aided by statistical tools, internalization of the risks of different tests would depend on provider recall and coincident identification of an association from the noise of a provider's experiences.

Table 9. Widest Range of Recurring (Annual) Benefit from Reduced Mortality from Cancer-Related Diagnostic Error

	Primary	Low	High
a) Harms Avoidable by the Phaseout Policy	325	24	4,244
b) Value Per Harm (VSLY using 3% discounting)	$1,650,181	$770,084	$2,511,942
c) Value Per Harm (VSLY using 7% discounting	$2,479,329	$1,157,020	$3,774,090
d) Percent Not Internalized at Baseline	95%	90%	100%
e) Total Benefit (VSLY using 3% discounting)	$508,931,983	$16,558,006	$10,661,349,657
f) Total Benefit (VSLY using 7% discounting	$764,649,367	$24,877,722	$16,018,239,255

However, due to our high degree of uncertainty about several of the parameters used to estimate the reduction in mortality risk from misdiagnosis related to cancer, we use a Monte Carlo simulation to determine a plausible range for total benefits by allowing each parameter (the rows in Table 5, the values per case in Table 8, and the internalization percentage in Table 9) to vary independently of the others. Whereas Table 9 implicitly assumes that all uncertain parameters share a joint probability distribution and are perfectly dependent (i.e., aligning all best- and worst-case scenarios across parameters), Table 10 below assumes certain parameters to be independent random variables as follows:

- the yearly number of premature deaths from misdiagnosis related to cancer follows a PERT distribution with a minimum, mean, and maximum taken from row (a) of Table 5;
- the probability that an IVD is offered as an LDT follows a PERT distribution with a minimum, mode, and maximum taken from row (c) of Table 5;
- the percent of such tests that would not be authorized by FDA follows a uniform distribution defined by the low and high estimates of row (e) of Table 5;
- the percent of such tests leading to a preventable misdiagnosis follows a uniform distribution defined by the low and high estimates of row (g) of Table 5;
- the treatment-to-diagnosis ratio follows a uniform distribution defined by the low and high of row (h) of Table 5;
- the values per harm using VSLYs that assume three and seven percent discounting follow triangular distributions with minimums, means, and maximums taken from rows (b) and (c), respectively, of Table 9; and

- the percent of risk of problematic IVDs not already internalized at baseline follows a uniform distribution defined by the low and high estimates from row (d) of Table 9.

Per HHS guidance (Ref. [42]), the low, primary, and high benefit estimates in Table 10 represent the 5th, 50th, and 95th percentiles from running the above simulation 100,000 times.

Table 10. Simulated Plausible Range of Recurring (Annual) Benefit from Reduced Mortality from Cancer-Related Diagnostic Error

	Primary	Low	High
e) Total Benefit (VSLY using 3% discounting)	$616,052,630	$191,389,437	$1,800,143,089
f) Total Benefit (VSLY using 7% discounting	$926,834,309	$286,994,300	$2,704,265,559

Given the uncertainty in this analysis and the implausibility of all best- and worst-case scenarios perfectly aligning across the uncertain parameters, we use the results from Table 10 to inform our total benefits estimates in II.E.4 "Summary of Benefits" and in Table 1, the main summary of benefits, costs, and transfers. As we explain in II.E.4 "Summary of Benefits" below, estimates in Table 1 are further adjusted to account for the enforcement discretion policy and the timing of the phase-in.

b. Cardiovascular Disease

Cardiovascular disease is prevalent in the U.S. According to the American Heart Association, in 2020, 48.6% of U.S. adults aged 20 and older had some form of cardiovascular disease, including coronary heart disease, heart failure, stroke, and hypertension (Ref. [43]). Additionally, the CDC notes that "heart disease is the leading cause of death for men, women, and people of most racial and ethnic groups in the United States" (Ref. [44]).

Table 11 below shows our estimated range for the number of harms from diagnostic error among patients with cardiovascular disease that we expect phasing out the general enforcement discretion approach for LDTs to avoid.

Using an estimate by Raisi-Estabragh et al. (2022) of about 20.6 million cardiovascular emergency department encounters in adults in the U.S. between 2016-2018 (Ref. [45]), we estimate about 6.9 million (= 20.6 million / 3) annual cardiovascular emergency department visits. It is likely that not all of these healthcare encounters involve initial diagnoses. However, IVDs are still used in visits concerning known conditions for monitoring of disease, prognosis, predicting treatment response, assessing the risk of developing a disease or disorder, and guiding patient management (Ref. [36]).

Excluding the state of New York proportionally by population,[36] we assume that about 6.5 million such cases are outside of NY and could thus potentially be managed using tests not approved by NYS CLEP. It is likely that some patients outside of the state of New York are also tested with LDTs approved by NYS CLEP and hence will not necessarily benefit from FDA's phaseout of enforcement discretion for premarket review requirements, but will still benefit from the phaseout of enforcement discretion for other requirements. According to Rohr et al. (2016), 62% of U.S. cardiology patients undergo IVD testing (Ref. [36]). Using test orders from a U.S. academic hospital system, Rychert et al. (2023) estimate that IVDs offered as LDTs are 3.9% of test order volume and 45% of distinct assays (Ref. [2]). In estimating the percent of patients tested with IVDs who are tested with IVDs offered as LDTs, we thus consider a range from 3.9% to 45%, with a primary estimate of 10%. Using the primary estimate, we estimate that about 0.4

[36] According to the Census Bureau as of July 1, 2022, the population of NY was 19,677,151, and the population of the U.S. was 333,287,557. We thus assume that about 5.9% (= 19,677,151 / 333,287,557) of CVD-related emergency department encounters are in NY. For the population estimates used, refer to: https://www.census.gov/quickfacts/fact/table/US/PST045222.

million U.S. (non-NY) patients with cardiovascular disease would rely on IVDs offered as LDTs (= 6,461,000 x 0.62 x 0.10).

As described in the previous section on harms related to diagnostic error among cancer patients, we consider a range of estimates of the number of these patients tested using IVDs offered as LDTs that will not be initially authorized by FDA following a premarket submission. As explained above, based on statistics from NYS CLEP on approved and denied applications, we consider initial rejection rates of 22%, 38%, and 54%.

In the central scenario with an expected rejection rate of 38% percent, about 152,000 patients with cardiovascular disease are managed using IVDs offered as LDTs that will not be authorized by FDA following a premarket submission—at least without changes. We assume that some of the time when these tests are used, they yield inaccurate results that would not occur using a test that could be authorized by FDA. Of these instances of inaccurate results, some might be caught during follow-up or other parts of the process of diagnosis before leading to harm from diagnostic error.

Lacking systematic data on the quality of applications for IVDs offered as LDTs rejected by NYS CLEP and these tests' roles in the process of diagnosis, we consider a range of rates at which avoidable errors might result from usage of problematic IVDs offered as LDTs: from a low of 25% to a high of 75%, with a central estimate of 50%. However, some of these errors might not have consequences for patient care if a patient would in any case be unable or unwilling to obtain treatment. Cardiovascular disease includes several different conditions, each of which might go untreated for various reasons. The American Heart Association reports treatment rates of high cholesterol (44.9%) and hypertension (52%), as well as the rate of diabetes patients with established atherosclerotic cardiovascular disease who are treated with a

statin (58.6%) (Ref. [43]). Based on these, we estimate that diagnostic error has treatment implications for 44.9% to 58.6% of patients, with a central estimate of 52%. Thus, using our central estimates, we expect the phaseout policy to avoid about 39,600 harms among patients with cardiovascular disease.

Table 11. Avoidable Harms Related to Diagnostic Error Among Cardiovascular Disease Patients

	Primary	Low	High
a) Annual US Cardiovascular Emergency Department Encounters (Non-NYS)	6,461,262	6,461,262	6,461,262
b) Percent Tested with IVDs	62%	62%	62%
c) Probability of IVD Being Offered as an LDT	10.0%	3.9%	45.0%
d) Patients Tested with IVDs Offered as LDTs (= a * b *c)	400,598	156,233	1,802,692
e) Percent of IVDs Offered as LDTs Not Authorized by FDA Following a Premarket Submission	38%	22%	54%
f) Tests Using Problematic IVDs Offered as LDTs (= d * e)	152,227	34,371	973,454
g) Percent Leading to Diagnostic Error	50%	25%	75%
h) Treatment-to-Diagnosis Ratio	0.52	0.449	0.586
i) Harms Avoidable by the Phaseout Policy (= f * g * h)	39,579	3,858	427,833

Harms from diagnostic error are diverse and can vary widely in severity, from avoidable inconvenience and expense to unnecessary treatments, disability, and premature mortality. As one example, between 2008 and early 2011, one laboratory sold over 160,000 StatinCheck tests designed to determine an individual's KIF6 genotype. This test was marketed as a way to determine a patient's response to statin drugs, based on the idea that patients with the Trp719Arg polymorphism of the KIF6 protein would have a greater reduction in cardiovascular disease (CVD) events when on statin therapy than patients without this polymorphism. However, research showed no association between the polymorphism and statin response (Refs. [13] [14]).

Additionally, in April 2011, FDA denied premarket approval of this test, citing lack of sufficient evidence of the safety and effectiveness of the test based in particular on clinical validity concerns.

Approximately 35% of patients in studies on CVD have the Trp719Arg polymorphism (Refs. [13] [14]). If 35% of the StatinCheck test recipients were identified as having the Trp719Arg polymorphism, then 56,000 patients may have been informed that they would respond better to statin therapy than other patients. If these patients received lower-potency statin treatment than is standard, a loss of health likely occurred, though medical expenditures were likely reduced. According to Conly et al. (2011), the use of high-potency statins results in an increase of 0.13 QALYs relative to the use of low-potency statins (Ref. [46]). Since this consists almost entirely of mortality effects, we value the health gains from high-potency statins in terms of life years. Conly et al. report life expectancy averages of 21.0 years for patients taking low-potency statins and 21.4 years for patients taking high-potency statins. Discounting at three and seven percent, this represents a gain of about 0.22 and 0.10 discounted life years, respectively, at the time of initiation of statin use. However, the use of high-potency statins in Canada costs CAD $1,200 more than low-potency statins (Ref. [46]). Converting to USD at the current rate of CAD $1.36 to USD $1.00, this is about $882. Based on a report prepared for the Department of Health and Human Services comparing international prescription drug prices, prices across all prescription drugs in Canada are about 44% of U.S. prices (Ref. [47]). We thus divide again by 0.44, resulting in a cost difference between high and low potency statins of about $2,005. Using a Value of a Statistical Life Year (VSLY) of $546,735 (the central VSLY that assumes three percent discounting), the value of lost health from using low-potency statins instead of high-potency statins is $121,086 (= $546,735 x 0.2215). The net lost benefit for each person using

low-potency statins is $119,080 (= $121,086 - $2,005), and the estimated total welfare losses are thus about $6.7 billion (= $119,080 x 56,000). Using a VSLY of $915,435 (the central VSLY that assumes seven percent discounting), the value of lost health from using low-potency statins instead of high-potency statins is $94,626 (= $915,435 x 0.1034). VSLYs are those projected for 2024 but using 2022 base year dollar values for consistency with the rest of this analysis. The net lost benefit for each person using low-potency statins is $92,621 (= $94,626 - $2,005), and the estimated total welfare losses over the period 2008-2011 are thus about $5.2 billion (= $92,621 x 56,000).

Thus, as a proxy for the value of an average harm from diagnostic error to a patient with a cardiovascular disease, we use $119,080 as our primary estimate given three percent discounting and $92,621 as our primary estimate given seven percent discounting. Further below, we also include estimates based on the low and high VSLY estimates.[37]

To estimate total benefit in Table 12 below, we multiply the estimated reduction in harms by the benefit per avoided harm and by the portion of relevant risk not already internalized in decision-making by medical providers and patients. Because providers who frequently order tests might note quality trends across different labs, we assume that only 95% of the risk of problematic IVDs offered as LDTs is not already internalized at baseline, with a range from 90-100%. Total internalization is unlikely, because without deliberate study of records aided by statistical tools, internalization of the risks of different tests would depend on provider recall and coincident identification of an association from the noise of a provider's experiences.

Table 12. Widest Range of Recurring (Annual) Benefit from Avoiding Harms from Diagnostic Error Related to Cardiovascular Disease

[37] Available at: https://aspe.hhs.gov/sites/default/files/documents/7f96080e2812365443347c1cca347188/standard-ria-values-2024.xlsx

	Primary	Low	High
a) Harms Avoidable by the Phaseout Policy	39,579	3,858	427,833
b) Value Per Harm (VQALY using 3% discounting)	$119,080	$54,501	$182,314
c) Value Per Harm (VQALY using 7% discounting	$92,621	$42,154	$142,037
d) Percent Not Internalized at Baseline	95%	90%	100%
e) Total Benefit (VQALY using 3% discounting)	$4,477,436,064	$189,248,233	$77,999,873,099
f) Total Benefit (VQALY using 7% discounting	$3,482,562,142	$146,372,612	$60,768,070,609

Due to our high degree of uncertainty about several of the parameters used to estimate the reduction in morbidity risk from diagnostic error related to cardiovascular disease, we use a Monte Carlo simulation to determine a plausible range for total benefits by allowing each parameter (the rows in Table 11 and the values per case and internalization percentage in Table 12) to vary independently of the others. Whereas Table 12 implicitly assumes that all uncertain parameters share a joint probability distribution and are perfectly dependent (i.e., aligning all best- and worst-case scenarios across parameters), Table 13 below assumes certain parameters to be independent random variables as follows:

- the percent of patients tested with IVDs who are tested with IVDs offered as LDTs follows a PERT distribution with a minimum, mode, and maximum taken from row (c) of Table 11;
- the percent of such tests that would not be authorized by FDA follows a uniform distribution defined by the low and high estimates of row (e) of Table 11;
- the percent of such tests leading to a preventable misdiagnosis follows a uniform distribution defined by the low and high estimates of row (g) of Table 11;
- the treatment-to-diagnosis ratio follows a PERT distribution with a minimum, mode, and maximum taken from row (h) of Table 11;

- the values per harm using VSLYs that assume three and seven percent discounting follow triangular distributions with minimums, means, and maximums taken from the low, primary, and high estimates in rows (b) and (c), respectively, of Table 12; and
- the percent of risk of problematic IVDs not already internalized at baseline follows a uniform distribution defined by the low and high estimates from row (d) of Table 12.

Per HHS guidance (Ref. [42]), the low, primary, and high benefit estimates in Table 13 represent the 5th, 50th, and 95th percentiles from running the above simulation 100,000 times.

Table 13. Simulated Plausible Range of Recurring (Annual) Benefit from Avoiding Harms from Diagnostic Error Related to Cardiovascular Disease

	Primary	Low	High
e) Total Benefit (VQALY using 3% discounting)	$5,430,362,350	$1,716,966,298	$15,579,610,547
f) Total Benefit (VQALY using 7% discounting	$4,233,288,851	$1,327,584,767	$12,131,010,945

Given the uncertainty in this analysis and the implausibility of all best- and worst-case scenarios perfectly aligning across the uncertain parameters, we use the results from Table 13 to inform our total benefits estimates in II.E.4 "Summary of Benefits" and in Table 1, the main summary of benefits, costs, and transfers. As we explain in II.E.4 "Summary of Benefits" below, estimates in Table 1 are further adjusted to account for the enforcement discretion policy and the timing of the phase-in.

c. Morbidity Due to Infections

Table 14 below shows our estimated range for the number of harms from diagnostic errors related to infections that we expect the phaseout policy to avoid. There are many kinds of infectious diseases. Because we cannot comprehensively analyze expected consequences of the phaseout policy with respect to all possible infectious diseases, we base our estimate of the

number of relevant cases on the CDC's statistics on selected national notifiable infectious diseases (Ref. [48]). For the year 2019, CDC reports 2,738,992 cases of those selected infectious diseases, over 93% of which are sexually transmitted infections. We believe this to be about half or more of all serious infectious diseases in the U.S., but we use this figure for lack of a comprehensive accounting of all other possible infectious diseases. Excluding the state of New York proportionally by population,[38] we assume that about 2,577,300 such cases occur outside of NY and could thus potentially involve tests not approved by NYS CLEP. It is likely that some patients outside of the state of New York are also tested with LDTs approved by NYS CLEP and hence would not necessarily benefit from the phaseout of enforcement discretion for premarket review requirements, but will still benefit from the phaseout of enforcement discretion for other requirements. According to Rohr et al. (2016), 64% of U.S. oncology and cardiology clinical decisions involve IVD testing (Ref. [36]), and due to lack of more directly relevant data, the oncology and cardiology estimate is extrapolated to the infectious disease context. Using test orders from a U.S. academic hospital system, Rychert et al. (2023) estimate that IVDs offered as LDTs are 3.9% of test order volume and 45% of distinct assays (Ref. [2]). In estimating the percent of patients tested with IVDs who are tested with IVDs offered as LDTs, we thus consider a range from 3.9% to 45%, with a primary estimate of 10%. Using the primary rate, we estimate that about 164,900 U.S. (non-NY) patients with infectious disease would rely on IVDs offered as LDTs (= 2,577,283 x 0.64 x 0.10).

As described in the earlier section on harms from diagnostic error related to cancers, we consider a range of estimates of the number of these patients tested using IVDs offered as LDTs

[38] According to the Census Bureau as of July 1, 2022, the population of NY was 19,677,151, and the population of the U.S. was 333,287,557. We thus assume that about 5.9% (= 19,677,151 / 333,287,557) of infection-related emergency department encounters are in NY. For the population estimates used, refer to: https://www.census.gov/quickfacts/fact/table/US/PST045222.

that will not be initially authorized by FDA following a premarket submission. As explained above in the section on cancers, based on statistics from NYS CLEP on approved and denied applications, we consider rejection rates of 22%, 38%, and 54% percent.

In the central scenario with an expected rejection rate of 38% percent, about 62,700 patients with infections are tested using IVDs offered as LDTs that will not be authorized by FDA following a premarket submission—at least without changes. We assume that some of the time when these tests are used, they yield inaccurate results that would not occur using a test that could be authorized by FDA. Of these instances of inaccurate results, some might be caught during follow-up or other parts of the process of diagnosis before leading to harm.

Lacking systematic data on the exact issues with applications for IVDs offered as LDTs initially rejected by NYS CLEP and these tests' roles in the process of diagnosis, we consider a range of rates at which avoidable error might result from usage of problematic IVDs offered as LDTs: from a low of 25% to a high of 75%, with a central estimate of 50%. However, some of these errors might not have consequences for patient care if a patient would in any case be unable or unwilling to obtain treatment. There are many kinds of infections, each of which might go untreated for various reasons. Based on treatment rates from Li et al. (2023) for chlamydia and gonorrhea among symptomatic and asymptomatic men and women in the US (Ref. [49]), and assuming equal numbers of men and women patients, overall treatment rates are about 36.42% for gonorrhea and 42.18% for chlamydia. Averaging between these two rates while weighting by their respective shares of notifiable disease cases (about three cases of chlamydia to one case of gonorrhea), we estimate that diagnostic error has treatment implications for 40.7% of infectious disease patients, with a range from 30-50%. Thus, using our central estimates, we expect the phaseout policy to avoid about 12,800 harms among patients with infections.

Table 14. Avoidable Harms from Diagnostic Error Related to Infections

	Primary	Low	High
a) Yearly U.S. Infections (Non-NYS)	2,577,283	2,577,283	2,577,283
b) Percent Tested with IVDs	64%	64%	64%
c) Probability of IVD Being Offered as an LDT	10.0%	3.9%	45.0%
d) Patients Tested with IVDs Offered as LDTs (= a * b *c)	164,946	64,329	742,258
e) Percent of IVDs Offered as LDTs Not Authorized by FDA Following a Premarket Submission	38%	22%	54%
f) Tests Using Problematic IVDs Offered as LDTs (= d * e)	62,680	14,152	400,819
g) Percent Leading to Diagnostic Error	50%	25%	75%
h) Treatment-to-Diagnosis Ratio	0.41	0.30	0.50
i) Harms Avoidable by the Phaseout Policy (= f * g * h)	12,761	1,061	150,307

Harms from diagnostic error are diverse and can vary widely in severity, from avoidable inconvenience and expense to unnecessary treatments, disability, and premature mortality. As over 93% of CDC national notifiable infectious disease cases are sexually transmitted diseases, we use average QALY loss from chlamydia and gonorrhea as a proxy for the value of an average harm from diagnostic error to a patient with an infectious disease. Based on discounted lifetime QALY loss estimates from Li et al. (2023) for chlamydia and gonorrhea among men and women in the US (Ref. [49]), and assuming equal numbers of men and women patients, average QALY losses are about 0.008 from gonorrhea and 0.024 from chlamydia. However, part of this health loss occurs during the acute infection, prior to diagnosis. Considering only the portions of health loss attributable to sequelae based on Figure 6 (Ref. [49]), these losses are about 0.007 from gonorrhea and 0.022 from chlamydia.[39] Averaging between these two diseases while weighting

[39] Li et al.'s Table 1 and Figure 3 imply that QALY gains due to treatment have the following central estimates: 0.008 for women with gonorrhea, 0.002 for men with gonorrhea, 0.061 for women with chlamydia, and 0.006 for men with chlamydia. With the incidence rates and populations from Li et al.'s Tables S-5 and S-6, the weighted average for gonorrhea is 0.005 and for chlamydia is 0.039. These estimates could represent upper bounds on QALY gains to be included in this document's Table 15, reflecting an assumption that misdiagnosis (and thus delayed treatment) produces as much harm as complete lack of treatment. Focusing only on expected values of

by their respective shares of notifiable disease cases (about three cases of chlamydia to one case of gonorrhea), we estimate that the average case entails a discounted lifetime QALY loss of about 0.0185. Health loss estimates by Li et al. consider lifetime sequelae and complications from lack of treatment such as pelvic inflammatory disease, but both gonorrhea and chlamydia are curable within a few days with antibiotics.[40] According to Malek et al. (2013), "delay in seeking care for STDs can [...] increase the likelihood of consequences such as infertility and chronic pelvic pain" (Ref. [50]).

Using a VQALY of $649,215 (the central VQALY that assumes three percent discounting), we thus assume that the value of lost health from an average infectious disease case without timely identification and treatment is about $12,000 (= $649,215 x 0.0185). Using a VQALY of $1,070,162 (the central VQALY that assumes seven percent discounting), the value of lost health is about $19,800. VQALYs are those projected for 2024 but using 2022 base year dollar values for consistency with the rest of this analysis.

Diagnostic error for infectious disease tests may lead to uncontrolled spread of communicable infectious diseases from contact with patients relying on false results from problematic IVDs. Our estimates do not account for harms from these downstream infections.

To estimate total benefit in Table 15 below, we multiply the estimated reduction in harms from diagnostic error by the benefit per avoided harm and by the portion of relevant risk not already internalized in decision-making by medical providers and patients. Because providers

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asymptomatic cases—which might be especially relevant to assessing the consequences of testing-related misdiagnosis—lack of treatment is associated with 0.002 lost QALY (gonorrhea central estimate) or 0.026 lost QALY (chlamydia central estimate). The omission of QALY loss associated with symptomatic cases may give such estimates a tendency toward understatement, but as before, the harm due to misdiagnosis-related delayed treatment is quantified as being equal to the harm of complete lack of treatment, thus generating a simultaneous tendency toward overstatement.

[40] See CDC on "Gonorrhea Treatment and Care" (https://www.cdc.gov/std/gonorrhea/treatment.htm), "Chlamydia Treatment and Care" (https://www.cdc.gov/std/chlamydia/treatment.htm), and "Sexually Transmitted Infections Treatment Guidelines, 2021" (https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf).

who frequently order tests might note quality trends across different labs, we assume that only 95% of the risk of problematic IVDs offered as LDTs is not already internalized at baseline, with a range from 90-100%. Total internalization is unlikely, because without deliberate study of records aided by statistical tools, internalization of the risks of different tests would depend on provider recall and coincident identification of an association from the noise of a provider's experiences.

Table 15. Widest Range of Recurring (Annual) Benefit from Avoiding Harms from Diagnostic Error Related to Infections

	Primary	Low	High
a) Harms Avoidable by the Phaseout Policy	12,761	1,061	150,307
b) Value Per Harm (VQALY using 3% discounting)	$11,995	$5,598	$18,259
c) Value Per Harm (VQALY using 7% discounting	$19,772	$9,227	$30,098
d) Percent Not Internalized at Baseline	95%	90%	100%
e) Total Benefit (VQALY using 3% discounting)	$145,414,428	$5,347,319	$2,744,440,950
f) Total Benefit (VQALY using 7% discounting	$239,700,470	$8,814,497	$4,523,923,748

Due to our high degree of uncertainty about several of the parameters used to estimate the reduction in morbidity risk from diagnostic error related to infectious diseases, we use a Monte Carlo simulation to determine a plausible range for total benefits by allowing each parameter (the rows in Table 14 and the values per case and internalization percentage in Table 15) to vary independently of the others. Whereas Table 15 implicitly assumes that all uncertain parameters share a joint probability distribution and are perfectly dependent (i.e., aligning all best- and worst-case scenarios across parameters), Table 16 below assumes certain parameters to be independent random variables as follows:

- the percent of patients tested with IVDs who are tested with IVDs offered as LDTs follows a PERT distribution with a minimum, mode, and maximum taken from row (c) of Table 14;
- the percent of such tests that would not be authorized by FDA follows a uniform distribution defined by the low and high estimates of row (e) of Table 14;
- the percent of such tests leading to a preventable misdiagnosis follows a uniform distribution defined by the low and high estimates of row (g) of Table 14;
- the treatment-to-diagnosis ratio follows a PERT distribution with a minimum, mode, and maximum taken from row (h) of Table 14;
- the values per harm using VQALYs that assume three and seven percent discounting follow triangular distributions with minimums, means, and maximums taken from the low, primary, and high estimates in rows (b) and (c), respectively, of Table 15; and
- the percent of risk of problematic IVDs not already internalized at baseline follows a uniform distribution defined by the low and high estimates from row (d) of Table 15.

Per HHS guidance (Ref. [42]), the low, primary, and high benefit estimates in Table 16 represent the 5th, 50th, and 95th percentiles from running the above simulation 100,000 times.

Table 16. Simulated Plausible Range of Recurring (Annual) Benefit from Avoiding Harms from Diagnostic Error Related to Infections

	Primary	Low	High
e) Total Benefit (VQALY using 3% discounting)	$189,393,046	$54,670,583	$577,904,403
f) Total Benefit (VQALY using 7% discounting	$311,957,235	$90,634,571	$953,299,062

Given the uncertainty in this analysis and the implausibility of all best- and worst-case scenarios perfectly aligning across the uncertain parameters, we use the results from Table 16 to inform our total benefits estimates in II.E.4 “Summary of Benefits” and in Table 1, the main

summary of benefits, costs, and transfers. As we explain in II.E.4 "Summary of Benefits" below, estimates in Table 1 are further adjusted to account for the enforcement discretion policy and the timing of the phase-in.

2. Non-Health Benefits

a. Spending on Inappropriate Use of Non-invasive Prenatal Screening (NIPS)

Non-invasive prenatal screening (NIPS) tests can provide information about the possibility of a fetus having certain genetic abnormalities that could result in a child being born with a serious health condition. Negative results can help pregnant individuals avoid the risks to fetal health of undergoing more invasive tests. However, as screening tests, positive results only indicate risk of a condition and require follow-up with diagnostic tests to confirm or rule out the suspected condition—in turn requiring discussion between patients and healthcare providers. NIPS test results should not be used by themselves to make critical healthcare decisions and should be discussed with a healthcare provider.

Given the increased use and marketing of these tests and recent media reports, FDA has warned the public of the risk of false results, inappropriate use, and inappropriate interpretation of NIPS test results, which might be addressed by phasing out the general enforcement discretion approach for LDTs. FDA is particularly concerned about reports of patients and health care providers that have made critical health care decisions based on results from these screening tests alone and without additional confirmatory testing, possibly related to misleading marketing.

Screening tests for extremely rare conditions caused by genetic microdeletions have generated significant revenue: "adding microdeletions can double what an insurer pays — from an average of $695 for the basic tests to $1,349 for the expanded panel, according to the health data company Concert Genetics" (Ref [15]). However, the five most common microdeletion tests

screen for conditions that affect only one in 5,000-20,000 births.[41] According to the NY Times, patients or their providers might lack the requisite understanding of NIPS to make informed purchase decisions: "doctors already order many tests during short prenatal care visits, meaning some probably thought little of tacking on a few more."[42] Additionally, the NY Times reveals evidence that patients or their providers might not understand that positive results from NIPS for rare conditions can be wrong up to 81 to 93 percent of the time (Ref. [15]). Misunderstanding by patients or their providers might result in avoidable distress and premature medical decisions or false reassurance. We consider that increased regulatory oversight might reduce spending on NIPS IVDs offered as LDTs to screen for a particular condition that have potentially unreliable, inaccurate, or misinterpreted results and require confirmatory diagnostic testing. Increased oversight of NIPS tests, including regarding labeling requirements, can help ensure such tests are appropriately labeled with transparent information regarding performance, clear instructions, and appropriate limitations.

A potentially unreliable, inaccurate, or misinterpreted test result imposes, at minimum, the monetary cost of the test to the patient or health care system payor and the burden of any resulting health consequences. We do not attempt to quantify any expected reduction in spending on these tests, but we note that the number of screening tests for microdeletions sold in 2020 was above 400,000, and patients or payors paid approximately an additional $654 for each expanded test.[43]

b. Reduction in Expenses from Lawsuits.

[41] Ibid.
[42] Ibid.
[43] Ibid.

Compliance with applicable legal requirements for IVDs offered as LDTs might also reduce the incidence of litigation related to problematic IVDs apart from that which stems directly from diagnostic error. We cannot quantify the welfare losses due to tort expenses that might be avoided by phasing out the general enforcement discretion approach for LDTs and do not include the avoidance of any such expenses in our estimate of benefits. However, we provide one case study concerning a COVID-19 test offered without emergency use authorization from FDA as an illustrative example.

On March 1st, 2022, Blue Cross and Blue Shield of Minnesota (Blue Cross or BCBSM) filed a lawsuit against COVID-19 testing laboratory GS Labs, LLC (GS Labs) to recover more than $10 million in overpayments made since the start of the pandemic (Ref. [51]). Blue Cross alleged violations of Minnesota consumer protection law, fraud, and ERISA violations. Among other issues, confusion between quality control processes specified by the test system manufacturer and the lab led GS Labs to issue a correspondence to patients about PCR tests that "inadvertently deviated from applicable laboratory standards for testing facilities" (Ref [52]). The case is currently ongoing (Refs. [51] and [53]).

In a 2022 report from the U.S. Chamber of Commerce Institute for Legal Reform (ILR), high costs in the tort system led to higher prices for other things in the economy. Compensation to claimants (when they win a case) only represents 53 percent of the total size of the tort system, while the remaining litigation and risk transfer costs make up about 47 percent of expenses in the system. In other words, for every $1.00 received by claimants, $0.88 was paid in legal and other costs ($1 / $1.88 =53%) (Ref. [54]). We assume that those total litigation and risk transfer costs are recaptured as savings when problems are prevented by compliance with applicable

requirements instead of corrected via litigation. In a $10 million dollar case, for example, litigation and risk transfer costs would be 47 percent of $10 million dollars or $4.7 million.

3. Summary of Benefits

Quantified health benefits include the avoidance of harms from diagnostic errors related to mortality (cancer and cardiovascular disease) and infections-related morbidity. Unquantified benefits include, among others, costs savings from avoiding payment for problematic IVDs, namely NIPS tests, and possible reduction in costs from lawsuits and reduction in costs to healthcare systems. We also note that we do not count individuals who may have contracted communicable infectious diseases from contact with patients relying on false results from problematic IVDs. We are not able to quantify the extent to which the phaseout policy might prevent the spread of communicable infectious diseases. Additionally, the phaseout policy might remove a disincentive for non-laboratory manufacturers, who do not have the benefit of enforcement discretion, to develop novel tests. These manufacturers may otherwise be discouraged from investing in novel tests due to the prospect of laboratory competitors offering IVDs as LDTs that claim to fulfill, equally effectively, the same needs without having to invest in meeting FDA requirements. This benefit would be distinct from avoiding patient harms by improving reliability in existing testing applications, since novel tests might offer new capabilities. We present total benefits and subtotal health and non-health benefits in Table 17.

Table 17. Total Undiscounted Benefits (Millions 2022$)

Health Benefits (VSLY 3%)		**Recurring Annual Benefits**		
Type	**Level**	Primary	Low	High
Cancer	Generalized	$616	$191	$1,800
Cardiovascular	Generalized	$5,430	$1,717	$15,580
Infections	Generalized	$176	$55	$502
Health Benefits (VSLY 7%)		**Recurring Annual Benefits**		
Type	**Level**	Primary	Low	High
Cancer	Generalized	$927	$287	$2,704

Cardiovascular	Generalized	$4,233	$1,328	$12,131
Infections	Generalized	$291	$91	$830
Total Sum of Benefits (VSLY 3%)		$6,223	$1,963	$17,881
Total Sum of Benefits (VSLY 7%)		$5,451	$1,705	$15,666

We expect benefits to begin to accrue two years after publication of the final phaseout policy, though we do not expect all estimated benefits to take place all at once. Instead, we assume that one-time benefits will occur evenly over Stages 1 to 5 of the final phaseout policy (year 3 to year 5). We also expect recurring benefits to begin to accrue at an incremental rate of 0%, 50%, 75%, and 100% for the first four years (Table 18).

Table 18. Undiscounted Potential Benefits Over Time (Primary Estimate in Millions 2022$, 20 years, 3% and 7%)

Stage	**Rate**		**Year**	**If VSLY based on 3% discounting**			**If VSLY based on 7% discounting**		
	One-time	**Recurring**		**One-time**	**Recurring**	**Total**	**One-time**	**Recurring**	**Total**
			1	$0	$0	$0	$0	$0	$0
1	0	0	2	$0	$0	$0	$0	$0	$0
2	1/3	1/2	3	$0	$3,111	$3,111	$0	$2,725	$2,725
3 & 4	1/3	3/4	4	$0	$3,151	$3,151	$0	$2,760	$2,760
4 & 5	1/3	1	5	$0	$4,420	$4,420	$0	$3,871	$3,871
	0	1	6	$0	$4,613	$4,613	$0	$4,041	$4,041
	:	:	:						
	0	1	20	$0	$5,899	$5,899	$0	$5,167	$5,167
Sum				$0	$91,718	$91,718	$0	$80,339	$80,339

However, as a result of exercising enforcement discretion with respect to premarket review and QS requirements, with the exception of requirements under 21 CFR 820, subpart M (Records), for currently-marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule, IVDs offered as LDTs will generally undergo review and comply with most QS requirements only in certain circumstances. However, FDA expects such IVDs offered as LDTs to be in compliance with other applicable requirements under the FD&C

Act and FDA regulations, including post market requirements, as discussed in the phaseout policy. We note that as described in section V.B.3 of the preamble, FDA intends to take targeted steps to address currently marketed IVDs offered as LDTs that are problematic. In particular, we intend to use available tools to identify and act against currently marketed IVDs offered as LDTs that specifically raise concerns, such as IVDs that are potentially inaccurate or poorly validated.

In order to account for this, we adjust estimated total benefits in each year—beginning with enforcement of QS and premarket review requirements—based on the proportions of IVDs falling within an enforcement discretion policy versus those that are not. IVDs falling within an enforcement discretion policy will not generally be expected to comply with premarket review and QS requirements (but will be expected to comply with all other applicable requirements as discussed in the phaseout policy). We thus assume that among patients using these IVDs, only half of the estimated potential benefits will be realized. The low and high benefits estimates reflect alternative assumptions that only 25% and 75% of benefits, respectively, will be realized among patients using IVDs falling within an enforcement discretion policy. In each year beginning with enforcement of QS and premarket review requirements in stage 3 and 4, we apply the following adjustment factor to estimated benefits:

$$adjustment = prop.of\ IVDs\ NOT\ falling\ within\ ED\ policy + 0.5 * prop.of\ IVDs\ falling\ within\ an\ ED\ policy$$

In Table 19, the resulting adjusted annualized benefit estimates using three and seven percent discounting are approximately $4.3 billion and $3.5 billion, respectively.

Table 19. Expected Benefits Over Time Accounting for Exercising Enforcement Discretion (Primary Estimate in Millions 2022$, 20 years)

Stage	Year	Proportions of IVDs by enforcement	c) Effect of ED	d) Adj. factor (= b + c*a)	Benefits (3% VSLY)	Benefits (7% VSLY)

		policy (premarket review and most QS requirements)		on benefits					
		a) With ED	b) Without ED			e) Without ED	With ED (=d*e)	f) Without ED	With ED (=d*f)
	1	0.918	0.082	0.5	0.541	$-	$-	$-	$-
1	2	0.818	0.182	0.5	0.591	$-	$-	$-	$-
2	3	0.729	0.271	0.5	0.636	$3,111	$3,111	$2,725	$2,725
3 & 4	4	0.650	0.350	0.5	0.675	$4,667	$3,151	$4,088	$2,760
4 & 5	5	0.580	0.420	0.5	0.710	$6,223	$4,420	$5,451	$3,871
	6	0.517	0.483	0.5	0.741	$6,223	$4,613	$5,451	$4,041
	7	0.462	0.538	0.5	0.769	$6,223	$4,786	$5,451	$4,192
	8	0.413	0.587	0.5	0.794	$6,223	$4,939	$5,451	$4,326
	9	0.369	0.631	0.5	0.816	$6,223	$5,075	$5,451	$4,446
	10	0.330	0.670	0.5	0.835	$6,223	$5,197	$5,451	$4,552
	11	0.295	0.705	0.5	0.853	$6,223	$5,305	$5,451	$4,647
	12	0.264	0.736	0.5	0.868	$6,223	$5,403	$5,451	$4,732
	13	0.236	0.764	0.5	0.882	$6,223	$5,490	$5,451	$4,808
	14	0.211	0.789	0.5	0.895	$6,223	$5,568	$5,451	$4,877
	15	0.188	0.812	0.5	0.906	$6,223	$5,638	$5,451	$4,938
	16	0.168	0.832	0.5	0.916	$6,223	$5,701	$5,451	$4,994
	17	0.149	0.851	0.5	0.925	$6,223	$5,758	$5,451	$5,044
	18	0.133	0.867	0.5	0.934	$6,223	$5,810	$5,451	$5,089
	19	0.118	0.882	0.5	0.941	$6,223	$5,856	$5,451	$5,130
	20	0.104	0.896	0.5	0.948	$6,223	$5,899	$5,451	$5,167
Sum						$107,344	$91,718	$94,026	$80,339
Present Value (Discount Rate matches VSLY)							$64,584		$37,177
Annualized Value (Discount Rate matches VSLY)							$4,341		$3,509

F. Costs

FDA is phasing out the general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs and be expected to meet applicable requirements. This phaseout is intended to help assure

the safety and effectiveness of IVDs offered as LDTs, while also accounting for other important public health considerations such as patient access and reliance.

FDA intends that the phaseout of enforcement discretion will occur over a four-year period in five key stages as described in section V.C of the preamble. For a few categories of IVDs manufactured by laboratories, FDA is adopting enforcement discretion policies with respect to some or all applicable requirements as described in sections V.B and C of the preamble.

When calculating the costs associated with each stage of the phaseout policy described in the preamble, we use wage information from the Bureau of Labor Statistics Occupational Employment and Wage Statistics.[44] Specifically, we use wage information for a specific industry: medical and diagnostic laboratories.[45]

The remainder of this section discusses the estimated cost of the phaseout policy by stage of the phaseout policy.[46] Section II.F.6 discusses additional cost considerations that we do not quantify.

1. Costs Under Stage 1

Beginning 1 year after the publication date of this final rule, FDA will expect laboratories[47] to comply with MDR requirements (requirements for adverse event reporting)

[44] https://www.bls.gov/oes/current/naics4_621500.htm
[45] NAICS code: 621500
[46] We use several sources to estimate costs associated with the phaseout policy. We use input from ICR packages for correction and removal reporting under Stage 1, but we rely on other sources such as previous RIAs or ERG reports to estimate costs for the other requirements. A major distinction between regulatory impact analysis (RIA) and Information Collection Request (ICR) is that the RIA bases estimates on external factors as yet unknown to FDA while ICR captures real-time data of the elements prescribed in regulations. In addition, the RIA considers affected entities according to specific requirements of regulations while the ICR includes a broader range for the number of respondents. Our estimates, therefore, may be different from the ICR package estimates because the RIA estimates costs of the rule in a different way compared as the costs of burden in the ICR package.
[47] In this section, when we use the word "laboratories," we refer to manufacturers who offer IVDs as LDTs that are within the scope of the phaseout policy.

under 21 U.S.C. 360i(a)-(c) and 21 CFR part 803, correction and removal reporting requirements under 21 U.S.C. 360i(g) and 21 CFR part 806, and QS requirements under § 820.198 (complaint files). During the first year following issuance of the final rule, laboratories will face costs associated with compliance with Stage 1, as well as costs associated with reading and understanding the rule in its entirety.

a. Reading and Understanding the Rule

We expect that laboratories affected by the phaseout policy will incur costs to read and understand the rule. We assume an average of one medical laboratory manager and one attorney at each entity will read the rule. Consistent with guidelines from the Department of Health and Human Services,[48] we assume that the reading speed of reviewers ranges from 200 to 250 words per minute. The final rule has approximately 150,000 words. The overall burden in hours (per reader) to read the rule ranges from 10.00 hours (= (150,000 words / 250 words per minute) / 60 mins per hour) to 12.50 hours (= (150,000 words / 200 words per minute) / 60 mins per hour). The mean hourly wages for managers and lawyers in this industry are $57.60 and $80.30, respectively.[49] Fully loaded wage rates are $115.20 an hour for managers and $160.60 an hour for lawyers (average: $137.90).[50] We assume that one to three employees will read the rule. The estimated learning costs per entity would range from $1,379.00 (=10.00 hours x $137.90 per hour x 1 employee) to $5,171.25 (=12.50 hours x $137.90 per hour x 3 employees), with a primary cost of $3,064.44 (=11.11 hours x $137.90 per hour x 2 employees). Multiplying this estimate by the total numbers of affected laboratories per year yields a total one-time cost for

[48] https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis
[49] NAICS code 621500, occupation codes 11-1021 for general and operations managers and 23-1011 for lawyers. Available from: https://www.bls.gov/oes/current/naics4_621500.htm
[50] Fully-loaded wages account for employee benefits and overhead on top of the hourly wage, calculated by doubling the published wage rate.

reading the rule between $0.81 million and $12.21 million, with a primary estimate of $3.62 million. The estimated total recurring cost ranges from $0.07 million to $0.98 million, with a primary estimate of $0.29 million (see Table 20).

Table 20. Costs of Reading and Understanding the Rule

	Primary	Low	High
Average reading speed (words/minute)	225	250	200
Length of preamble & codified (words)	150,000	150,000	150,000
Hours	11.11	10.00	12.50
Number of employees to read rule	2	1	3
Labor cost of hourly employee	$137.90	$137.90	$137.90
Per-laboratory cost	$3,064.44	$1,379.00	$5,171.25
Number of affected laboratories	1,181	590	2,362
Number of new laboratories per year	94	47	189
Total One-time Costs (millions)	**$3.62**	**$0.81**	**$12.21**
Total Recurring Costs (millions)	**$0.29**	**$0.07**	**$0.98**

Note: Product across table may not be exact due to rounding.

b. Medical Device Reporting

Under Stage 1, FDA expects laboratories to comply with MDR requirements under 21 U.S.C. 360i(a)-(c) and 21 CFR part 803. In estimating the costs of compliance for laboratories, we use a similar approach to the *Medical Device Reporting: Electronic Submission Requirements* final regulatory impact analysis (Ref. [55]). We expect that laboratories will face one-time costs associated with establishing a reporting system for laboratories for which, at baseline, the requirement to have such systems generally has not been enforced. We also expect new laboratories to enter the market each year, so we assume that the new entities will incur recurring costs associated with establishing a reporting system.

We expect laboratories to establish standard operating procedures (SOPs) in response to the MDR requirements. We estimate it will take 1 – 3 management employees with an hourly wage of $61.36 ($122.72 fully-loaded) 8 – 12 hours each to establish a laboratory's SOP and

train the appropriate people on the new procedures. Multiplying these estimates, we estimate the one-time costs of modifying SOPs to be between $0.58 million and $10.43 million, with a primary estimate of $2.90 million. We estimate the recurring costs to range from $0.05 million to $0.83 million, with a primary estimate of $0.23 million. See Table 21.

We expect laboratories to install and validate e-Submitter software for the purposes of complying with MDR requirements. We expect this task to take a single computer and information system manager 48 to 56 hours, working at an hourly wage of $79.72 ($159.44 fully loaded). Multiplying by the number of affected entities, we estimate the one-time costs of installing and validating e-Submitter software to be between $4.52 million and $21.09 million, with a primary estimate of $9.79 million. We estimate the recurring costs to be between $0.36 million to $1.69 million, with a primary estimate of $0.78 million.

We expect 0.6% of covered laboratories to establish Health Level Seven (HL7) Individual Case Study Report (ICSR) capability (Ref. [55]).[51] We expect this task to take a single computer and information system manager 48 to 52 hours, working at an hourly wage of $79.72 ($159.44 fully loaded). Multiplying by the small fraction of laboratories that we expect to establish such capabilities, we estimate the one-time costs to range between $0.03 million to $0.12 million, with a primary estimate of $0.06 million. We estimate the recurring costs to be between $0.002 million to $0.01 million, with a primary estimate of $0.005 million.

We expect laboratories to acquire an e-certificate from a third-party system to commence medical device reporting. We estimate that there is a small one-time search cost of acquiring the e-certificate of $20. Multiplied by the number of affected entities, we estimate the one-time costs of acquiring an e-certificate to range from $0.01 million to $0.05 million,

[51] We divide the number of entities that would use the HL7ICSR (125 entities) by 20,100 medical device manufacturers and importers covered by the MDR regulation.

with a primary estimate of $0.02 million. We estimate the recurring costs to range from $0.001 million to $0.004 million, with a primary estimate of $0.002 million.

We also expect a small recurring cost associated with the payment of an annual fee to maintain e-certification in the reporting system. We anticipate an annual $10 search cost that applies to each affected laboratory. Multiplying by the number of total laboratories, we estimate this recurring cost to range from $0.01 million to $0.02 million, with a primary estimate of $0.01 million.

Finally, we expect a recurring cost associated with filing and submitting MDRs. We estimate it will take computer and information system managers 430 hours,[52] working with an hourly wage of $79.72 ($159.44 fully loaded). Multiplying by the number of affected entities, we estimate this recurring cost to range from $40.47 million to $161.88 million, with a primary estimate of $80.94 million.

Overall, we expect the total one-time costs for complying with MDR requirements in Stage 1 of the phaseout policy to range from $5.36 million to $32.57 million, with a primary estimate of $13.21 million. The estimated total recurring costs range from $40.91 million to $164.55 million, with a primary estimate of $82.03 million. See Table 21.

Table 21. Costs of Medical Device Reporting

		Primary	Low	High
One-time/Annual				
Establish SOPs	Hours	10	8	12
	Wage	$122.72	$122.72	$122.72
	Employees	2	1	3

[52] We use annual reporting and record keeping burdens from a prior analysis of medical device reporting. In particular, we use the total number of hours associated with creating a medical device report, multiplied by the average number of reports per respondent (Ref. [55]). We assume that each affected laboratory will list an average number of 67 product listings, an average number of 2 modified product listings, and an average number of 6 new product listings per year, based on our estimates discussed in section II.D.1. We also assume 1.4 MDRs per listing.

	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	One-time Subtotal (millions)	*$2.90*	*$0.58*	*$10.43*
	Recurring Subtotal (millions)	*$0.23*	*$0.05*	*$0.83*
Install and Validate e-Submitter Software	Hours	52	48	56
	Wage	$159.44	$159.44	$159.44
	Employees	1	1	1
	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	One-time Subtotal (millions)	*$9.79*	*$4.52*	*$21.09*
	Recurring Subtotal (millions)	*$0.78*	*$0.36*	*$1.69*
Establish HL7ICSR capability	Hours	50	48	52
	Wage	$159.44	$159.44	$159.44
	Employees	1	1	1
	Entities affected	7	4	14
	New entities per year	1	0	1
	One-time Subtotal (millions)	*$0.06*	*$0.03*	*$0.12*
	Recurring Subtotal (millions)	*$0.005*	*$0.002*	*$0.01*
Acquiring e-Certificate	Search cost	$20.00	$20.00	$20.00
	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	One-time Subtotal (millions)	*$0.02*	*$0.01*	*$0.05*
	Recurring Subtotal (millions)	*$0.002*	*$0.001*	*$0.004*
Recurring Annual				
Maintaining Certificates	Search cost	$10.00	$10.00	$10.00
	Entities affected	1,181	590	2,362
	Recurring Subtotal (millions)	*$0.01*	*$0.01*	*$0.02*
Filing and submitting MDRs	Hours	430	430	430
	Wage	$159.44	$159.44	$159.44
	Entities affected	1,181	590	2,362
	Recurring Subtotal (millions)	*$80.94*	*$40.47*	*$161.88*
Total One-time Costs (millions)		**$13.21**	**$5.36**	**$32.57**
Total Recurring Costs (millions)		**$82.03**	**$40.91**	**$164.55**

Notes: Total one-time and recurring costs include both costs to industry and FDA. See section II.G for FDA review costs of MDRs.

c. Correction and Removal Reporting

Under Stage 1, FDA expects laboratories to comply with correction and removal reporting requirements under 21 U.S.C. 360i(g) and 21 CFR part 806. In estimating the costs of

compliance for laboratories, we use information from the 2023 FDA notice: *Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals* (Ref. [56]).[53] We expect that the majority of correction and removal reporting costs will be recurring costs associated with creating correction and removal reports. At baseline, the requirement to create such reports generally has not been enforced.

We expect 50% of laboratories to purchase a digital verification certificate to assist with correction and removal reporting (Ref. [56]).[54] We expect this certificate to cost $50. Multiplying by the number of affected entities, we expect a one-time cost of purchasing a digital verification certificate to range from $0.01 million to $0.06 million, with a primary estimate of $0.03 million. Multiplying by the number of new entities per year, we expect a recurring cost of purchasing a digital verification certificate to range from $1,181 to $4,723, with a primary estimate of $2,362.

We expect laboratories to incur a recurring cost associated with correction and removal reporting requirements. We assume it will take a single general/operations manager working at an hourly wage of $57.60 ($115.20 fully-loaded) 10 hours to create a single correction and removal report. The 2023 FDA notice *Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals* acknowledged 1,033 correction and removal reports per year. In

[53] The ICR package of corrections and removals (OMB control number 0910-0359) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202309-0910-003

[54] We expect that the other 50% of laboratories not using the electronic submission gateway (ESG) would either already have a digital certificate from previous submission or will submit reports of corrections and removals to FDA via mail or email. Specifically, up to 45% will submit using a digital certificate that they already purchased or via email and about 5% of laboratories will submit their reports via mail or email. The burden will be lower for those already purchased the ESG and the burden may be higher for those submitting via mail or email. Due to lack of data, we are unable to quantify the costs for those not using the ESG that we may underestimate the costs of correction and removal reporting affected by this phaseout policy.

2020, the U.S. Census Statistics of U.S. Businesses (SUSB) estimated there were approximately 9,338 medical device manufacturing establishments in the U.S.[55] These numbers suggest that there are approximately 0.11 correction and removal reports per year per entity. We assume that ratio is the same for laboratories and apply the ratio to the total number of affected entities. Multiplying all elements together, we estimate the recurring cost of correction and removal reporting to range between $0.07 million to $0.30 million, with a primary estimate of $0.15 million.

Overall, we expect the total one-time costs for correction and removal reporting in Stage 1 of the phaseout policy to range between $0.01 million to $0.06 million, with a primary estimate of $0.03 million. The estimated total recurring costs range from $0.08 million to $0.30 million, with a primary estimate of $0.15 million. See Table 22.

Table 22. Costs of Correction and Removal Reporting

		Primary	Low	High
One-time/Annual				
Digital Verification Certificate	Flat fee	$50.00	$50.00	$50.00
	Entities affected	590	295	1,181
	New entities per year	47	24	94
	One-time Subtotal (millions)	*$0.03*	*$0.01*	*$0.06*
	Recurring Subtotal	*$2,362*	*$1,181*	*$4,723*
Recurring Annual				
Reporting	Hours per report	10	10	10
	Number of reports per entity	0.11	0.11	0.11
	Wage	$115.20	$115.20	$115.20
	Entities affected	1,181	590	2,362
	Recurring Subtotal (millions)	*$0.15*	*$0.07*	*$0.30*
Total One-time Costs (millions)		**$0.03**	**$0.01**	**$0.06**
Total Recurring Costs (millions)		**$0.15**	**$0.08**	**$0.30**

[55] We select NAICS code 33911: Medical Equipment and Supplies Manufacturing from the full dataset available at: https://www.census.gov/data/datasets/2020/econ/susb/2020-susb.html

d. Complaint Files

Under Stage 1, FDA will expect laboratories to comply with quality system (QS) requirements under 21 CFR part 820.198 (complaint files).[56] In estimating the costs of complaint files, we use number of annual labor hours and proportion of types of labor (from vice president to clerical staff) needed to comply with complaint file requirements (Ref. [57]).[57] We also use wage rates to estimate costs for affected entities (see Table 27). We multiply the labor hours by appropriate wage rates and number of affected entities to estimate costs of complaint files. The estimated total one-time costs for complaint files range from $0.60 million to $6.04 million, with a primary estimate of $2.11 million. The estimated total recurring costs range from $0.01 million to $0.05 million, with a primary estimate of $0.02 million.

Table 23. Costs of Complaint Files

		Primary	Low	High
One-time				
820.198 Complaint files	Hours	14	8	20
Entities affected		1,181	590	2,362
Recurring Annual				
820.198 Complaint files	Hours	2	1	2
New entities per year		94	47	189
Total One-time Costs (millions)		**$2.11**	**$0.60**	**$6.04**
Total Recurring Costs (millions)		**$0.02**	**$0.01**	**$0.05**

2. Costs Under Stage 2

Under Stage 2, FDA will expect that laboratories comply with requirements not covered during other stages of the phaseout policy beginning 2 years after the publication of the phaseout policy. These requirements include registration and listing requirements (21 U.S.C. 360 and 21

[56] The ICR package of QS regulation (OMB control number 0910-0073) is available at: https://www.reginfo.gov/public/do/PRAViewDocument?ref_nbr=202309-0910-003

[57] We assume half of the labor hours would be for complaint files and the other half of the labor hours would be for other activities under subpart M.

CFR part 807, excluding subpart E), labeling requirements (21 U.S.C. 352 and 21 CFR parts 801 and 809, subpart B), and investigational use requirements (21 U.S.C. 360j(g) and 21 CFR part 812).[58]

a. Registration and Listing

Under Stage 2, FDA expects laboratories to comply with registration and listing requirements under 21 U.S.C. 360 and 21 CFR part 807 (excluding subpart E). In estimating the costs of compliance for laboratories, we use a similar approach to the 2016 *Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs That Are Regulated Under a Biologics License Application, and Animal Drugs* final regulatory impact analysis (Ref. [58]).[59] We anticipate one-time costs associated with registration and listing requirements and recurring costs associated with re-registration.

We expect the registration and listing will take a general/operations manager 3 hours, working at a wage of $57.60 ($115.20 fully loaded), to complete registration for a single establishment and to list that establishment's IVDs offered as LDTs.[60] We also expect that annual re-registration and listing updates will take a general/operations manager 1 hour. Multiplying by the numbers of affected entities per year, we expect total one-time costs for registration and listing requirements to range between $0.20 million and $0.82 million, with a

[58] We anticipate that costs for compliance with any other requirements under Stage 2 such as mandatory recall orders under section 518(e) of the FD&C Act, or notification orders under section 518(a) of the FD&C Act would only be triggered under certain circumstances. Therefore, the costs are likely to be minimal compared to the costs for compliance with the requirements listed below. In addition, if requirements listed below are appropriately satisfied, these other requirements generally should not become applicable.

[59] The ICR package of registration and listing (OMB control number 0910-0625) is available at: https://www.reginfo.gov/public/do/PRAViewDocument?ref_nbr=202206-0910-003

[60] We assume that each affected laboratory will list an average number of 67 product listings and an average number of 6 new product listings per year, based on our estimates discussed in section II.D.1.

primary estimate of $0.41 million. The estimated total recurring costs range from $0.08 million to $0.34 million, with a primary estimate of $0.17 million. See Table 24.

Table 24. Costs of Registration and Listing

		Primary	Low	High
One-time/Annual				
Initial registration and listing of IVDs offered as LDTs	Hours	3	3	3
	Wage	$115.20	$115.20	$115.20
	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	One-time Subtotal (millions)	*$0.41*	*$0.20*	*$0.82*
	Recurring Subtotal (millions)	*$0.03*	*$0.02*	*$0.07*
Recurring Annual				
Re-registration	Hours	1	1	1
	Wage	$115.20	$115.20	$115.20
	Entities affected	1,181	590	2,362
	Recurring Subtotal (millions)	*$0.14*	*$0.07*	*$0.28*
Total One-time Costs (millions)		**$0.41**	**$0.20**	**$0.82**
Total Recurring Costs (millions)		**$0.17**	**$0.08**	**$0.34**

b. Labeling

Under Stage 2, FDA expects laboratories to comply with labeling requirements under 21 U.S.C. 352, 21 CFR part 801, and 21 CFR part 809, subpart B. We anticipate one-time and recurring costs associated with revising existing labeling.

We expect it will take a general/operations manager, working at a wage of $57.60 ($115.20 fully-loaded), [61] 8 to 54 hours (with a primary estimate of 31 hours) for regulatory affairs personnel and production personnel per laboratory to redesign existing labeling for IVDs offered as LDTs to comply with labeling requirements (Ref. [59]).[62] Manufacturers would spend

[61] NAICS code 621500, occupation codes 11-1021 for general and operations managers. Available from: https://www.bls.gov/oes/current/naics4_621500.htm

[62] The ICR package of medical device labeling requirements (OMB control number 0910-0485) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202308-0910-004

these hours to revise the labeling, including among other things, to perform internal review of the new content, to prepare and proofread new artwork, to replace labeling in the production system, and to submit the file to the agency. Multiplying by the number of expected entities, we expect the one-time cost of revising existing labeling to range between $0.54 million and $14.69 million, with a primary estimate of $4.22 million.[63] Multiplying the estimates by the number of new entities per year, we expect the recurring cost to range between $0.04 million to $1.18 million, with a primary estimate of $0.34 million. See Table 25.

Table 25. Costs of Labeling

		Primary	Low	High
Revise existing labeling	Hours	31	8	54
	Wage	$115.20	$115.20	$115.20
	Entities affected	1,181	590	2,362
	New entities per year	94	47	189
	One-time Subtotal (millions)	*$4.22*	*$0.54*	*$14.69*
	Recurring Subtotal (millions)	*$0.34*	*$0.04*	*$1.18*
Total One-time Costs (millions)		**$4.22**	**$0.54**	**$14.69**
Total Recurring Costs (millions)		**$0.34**	**$0.04**	**$1.18**

c. Investigational Use Requirements

Under Stage 2, FDA expects laboratories to comply with investigational use requirements under 21 U.S.C. 360j(g) and 21 CFR part 812. Investigational medical devices (i.e., that are the object of a clinical investigation or research involving one or more subjects to determine device safety and/or effectiveness) that have an approved investigational device exemption (IDE) application, that are considered to have an approved IDE under 21 CFR part 812.2(b), or that are exempt from most of the requirements in 21 CFR part 812 under 21 CFR 812.2(c), are

[63] As discussed in section II.D.1, we assume each affected laboratory offers 67 IVDs as LDTs and will offer 6 new IVDs as LDTs per year.

exempted from various other requirements under the FD&C Act and FDA's regulations, such as premarket approval. We anticipate one-time and annual costs associated with complying with investigational device exemption requirements under 21 U.S.C. 360j(g) and 21 CFR part 812.[64]

We expect the cost of developing an IDE application for an IVD offered as an LDT to be $48,000 (Ref. [60])[65].We assume two percent of the existing IVDs offered as LDTs are investigational, based on extrapolation of internal information from NYSDOH regarding the percent of IVD submissions they receive that are for investigational IVDs offered as LDTs (Ref. [28]). NYSDOH receives IVD submission packages for IVDs offered as LDTs that are not "designated as FDA-cleared, approved, or exempt," (Ref. [29]) and these submission packages include clinical trial tests as well as high, moderate, and low risk tests offered for clinical use, based on NYSDOH criteria. Over a two-year period, approximately two percent of IVD submission packages received by NYSDOH were for clinical trial IVDs per NYSDOH criteria.

Not all investigational IVDs require an IDE application.[66] Based on the number of IVD IDE submissions and the number of IVD premarket submissions that FDA received over a four-year period, we estimate that we receive about 13.5 IVD IDE submissions for every 100 premarket submissions. Therefore, we estimate that about 13.5% of investigational IVDs

[64] The ICR package of investigational device exemptions (OMB control number 0910-0078) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202210-0910-013

[65] IDE requirements in 21 CFR part 812 include certain requirements distinct from the requirement for approval of an IDE application, such as certain recordkeeping and labeling requirements. We anticipate that costs for compliance with these other requirements, where applicable, would be minimal compared to the costs discussed in this subsection for preparing and submitting an IDE application. These costs may be overestimated as the cited source reflects costs of IDE applications for all devices.

[66] Investigations of certain categories of devices are exempt from most requirements in 21 CFR part 812. See 21 CFR 812.2(c). Moreover, certain categories of investigations are considered to have an approved IDE application. See 21 CFR 812.2(b).

offered as LDTs that would later be subject to premarket review would first submit an IDE application. We estimate that 50% of IVDs are exempt from premarket notification and 50% require a premarket submission. Applying these factors, we estimate that 6.75% (which represents 50% x 13.5%) of investigational IVDs would require an IDE application.

The number of IDE applications for IVDs currently offered as an LDT can be estimated by multiplying the percent of investigational IVDs currently offered as an LDT (2%) by the percent of investigational IVDs that would require an IDE application (6.75%) by the number of affected IVDs offered as LDTs.

We also expect there would be new investigational IVDs introduced every year, at a rate of anywhere between 1% and 100% of new IVDs. To account for our uncertainty, we assume that the mean value between 1% and 100% or 50% of the new IVDs would be investigational. As described above, we estimate that 6.75% of investigational IVDs would require an IDE.

Multiplying the cost estimates from literature by the relevant percentages and number of affected IVDs offered as LDTs, we expect the total one-time costs of preparing and submitting IDE applications for the existing IVDs offered as LDTs to range between $2.56 million and $10.25 million, with a primary estimate of $5.13 million. Table 26 shows the estimated annual costs, which range from $6.20 million to $24.79 million, with a primary estimate of $12.40 million.

Table 26. Costs of Complying with Investigational Use Requirements

		Primary	Low	High
One-time				
Total cost of preparing/	Inflation-adjusted estimate from literature	$48,000	$48,000	$48,000

submitting IDE	Percent of IVDs offered as LDTs that are investigational	2	2	2
	Percent of investigational IVDs offered as LDTs that require submission of IDE application	6.75	6.75	6.75
	IVDs currently offered as LDTs affected	79,114	39,557	158,227
	One-time Subtotal (millions)	*$5.13*	*$2.56*	*$10.25*
Annual				
Total cost of preparing/ submitting IDE	Inflation-adjusted estimate from literature	$48,000	$48,000	$48,000
	Percent of IVDs offered as LDTs that are investigational	50	50	50
	Percent of investigational IVDs offered as LDTs that require submission of IDE application	6.75	6.75	6.75
	New IVDs offered as LDTs per year	7,652	3,826	15,303
	Annual Subtotal (millions)	*$12.40*	*$6.20*	*$24.79*
Total One-time Costs (millions)		**$7.45**	**$3.73**	**$14.90**
Total Annual Costs (millions)		**$18.02**	**$9.01**	**$36.03**

Notes: Total one-time and recurring costs include both costs to industry and FDA. See section II.G for FDA review costs of IDEs.

3. Costs Under Stage 3

Beginning 3 years after the publication of this final rule, FDA will expect compliance with the device current good manufacturing practices (CGMP) requirements of the QS requirements under 21 U.S.C. 360j(f) and 21 CFR part 820 (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1).

However, for LDTs, FDA expects compliance with some, but not all, of the QS requirements. As described in section V.C.3 of the preamble, for these LDTs, FDA expects compliance with:

- design controls under 21 CFR 820.30;
- purchasing controls (including supplier controls) under 21 CFR 820.50;

- acceptance activities (receiving, in-process, and finished device acceptance) under 21 CFR 820.80 and 21 CFR 820.86;
- corrective and preventative actions (CAPA) under 21 CFR 820.100; and
- records requirements under 21 CFR part 820, subpart M (including requirements regarding complaint files under 21 CFR 820.198, for which FDA expects compliance during stage 1 of the phaseout policy).

As further described in section V.C.3 of the preamble, for IVDs that are within the scope of the phaseout policy but for which all manufacturing activities do not occur within a single laboratory, or which are transferred outside of that single laboratory, FDA also expects compliance with the other QS requirements under 21 U.S.C. 360j(f) and 21 CFR part 820. We lack evidence to quantify the numbers of such IVDs. To account for uncertainty, we consider different assumptions for low, primary, and high estimates. To estimate a lower bound estimate, we first assume that for all IVDs within the scope of the phaseout policy, all manufacturing activities occur within a single laboratory and, therefore, have zero costs associated with the QS requirements other than those listed above. For an upper bound estimate, we assume that all manufacturing activities do not occur within a single laboratory for any IVD within the scope of the phaseout policy and, therefore, have costs associated with all QS requirements. Since we expect there to be a mix of these two extremes within the scope of the phaseout policy, we use an average of the lower and upper bound estimates for our primary estimate.

In estimating the costs of compliance for laboratories, we use number of annual labor hours and proportion of types of labor (from vice president to clerical staff) needed to comply with each relevant provision of 21 CFR part 820. We also use wage rates to estimate costs of

complying with these provisions for affected entities (see Table 27).[67] Table 28 shows the number of labor hours for compliance with each provision of Part 820 (Ref. [57]). We multiply the labor hours by appropriate wage rates and number of affected entities to estimate costs of compliance with the QS requirements under this stage.[68]

Since FDA generally intends to exercise enforcement discretion with respect to QS requirements (other than requirements regarding records) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in the preamble, we anticipate one-time costs of compliance with records requirements other than complaint files from existing IVDs offered as LDTs and recurring costs from new IVDs offered as LDTs under this stage. In addition, we estimate that the number of affected entities for Stage 3 is lower than Stages 1 and 2 as FDA intends to exercise enforcement discretion with respect to QS requirements (other than requirements regarding records) for LDTs manufactured and performed by a laboratory integrated within a health care system to meet an unmet need of patients receiving care within the same healthcare system. Further, it is our understanding, based on consultation with NYS CLEP, that compliance with NYS CLEP's clinical laboratory standards (which exceed CLIA requirements in certain respects) and its premarket review requirements collectively could generally satisfy these subparts of the QS regulations except as to certain aspects of design control documentation. Therefore, FDA does not anticipate significant additional burden with respect to compliance with these QS requirements for laboratories offering LDTs approved by NYS CLEP. As discussed in appendix A, we estimate 12.1 percent of new premarket submissions for affected tests will be

[67] All wage rates are doubled to account for overhead costs. Available from: https://www.bls.gov/oes/current/naics4_621500.htm

[68] As discussed in section II.D.1, we assume each affected laboratory offers 67 IVDs as LDTs and will offer 6 new IVDs as LDTs per year.

reviewed by NYS CLEP. For the purpose of estimating costs associated with compliance with Quality System requirements, we extrapolate this to the affected laboratories, estimating that 12.1 percent of affected laboratories (1,181) will have their LDTs reviewed by NYS CLEP. We also estimate that 40 to 70 percent of LDTs from the high complexity laboratories integrated within health care systems (459) are likely to be for unmet needs. We therefore estimate the affected laboratories incurring costs under Stage 3 to be 786 (=1,181 – 1,181*0.121 – 459*0.55).

We expect the total one-time costs for QS requirement (records other than complaint files under 21 CFR 820.198) in Stage 3 of the phaseout policy to range from $0.40 million to $4.02 million, with a primary estimate of $1.41 million. The total recurring costs are estimated to range from $1.94 million to $124.01 million, with a primary estimate of $24.66 million. See Table 28.

Table 27. Medical and Diagnostic Laboratories Industry Wage Rates for Selected Labor Categories

Labor Category	Wages (/hour)	NAICS	OCC Code
Vice president	$59.68	621500	11-1000
Upper management	$76.38	621500	11-2000
Middle management	$66.83	621500	11-3000
Technical	$30.36	621500	29-0000
Admin support	$32.67	621500	43-6011
Clerical	$18.37	621500	43-4000

Table 28. Costs of Compliance with Quality System Requirements

		Primary	Low	High
One-time/Annual				
820.20(a) Quality Policy	Hours	8	0	24
820.20(b) Organization	Hours	6	0	20
820.20(d) Quality Planning	Hours	14	0	40
820.20(e) Quality System Procedures	Hours	14	0	40
820.22 Quality Audit	Hours	8	0	24
820.25 Personnel, establish procedures for identifying training needs	Hours	8	0	24

820.25 Personnel, train in CGMP revisions	Hours	50	0	290
820.40 Document Controls	Hours	14	0	40
820.60 Identification and Traceability	Hours	8	0	24
820.72, 820.75 Inspection, measuring, and test equipment, process validation	Hours	23	0	72
820.70(i) Automated Processes	Hours	14	0	40
820.90 Nonconforming Product	Hours	14	0	40
820.140 Handling	Hours	8	0	24
820.200 Servicing	Hours	14	0	40
820.30(a) General	Hours	200	30	560
820.50(a) Assessment of Suppliers and Contractors	Hours	75	25	125
820.100 Corrective and Preventive Action	Hours	28	16	40
820.150 Storage	Hours	15	8	24
820.198 Complaint Files	Hours	14	8	20
Entities affected		786	393	1,571
New entities per year		63	31	126
Recurring Annual				
820.20(a) Quality Policy	Hours	1	0	2
820.20(b) Organization	Hours	1	0	2
820.20(c) Management Review	Hours	8	0	24
820.20(d) Quality Planning	Hours	4	0	10
820.20(e) Quality System Procedures	Hours	4	0	10
820.22 Quality Audit	Hours	1	0	2
820.25 Personnel, maintain procedures	Hours	1	0	2
820.40 Document Controls	Hours	2	0	4
820.60 Identification and Traceability	Hours	1	0	2
820.72, 820.75 Inspection, measuring, and test equipment, process validation	Hours	4	0	13
820.70(i) Automated Processes	Hours	2	0	4
820.90 Nonconforming Product	Hours	2	0	4
820.140 Handling	Hours	1	0	2
820.200 Servicing	Hours	2	0	4
820.30(a) General	Hours	20	3	56
820.30(b) Design and Development Planning	Hours	216	32	520
820.30(e) Design Review	Hours	942	82	2,574
820.30(f) Design Verification	Hours	1,681	249	4,047
820.30(h) Design Transfer	Hours	43	6	104
820.30(i) Design Changes	Hours	378	56	910
820.30(j) Design History File	Hours	22	3	52
820.50(a) and (b) Purchasing control	Hours	159	98	233

820.100 Corrective and Preventive Action	Hours	3	2	4
820.150 Storage	Hours	2	1	2
820.198 Complaint Files	Hours	2	1	2
New entities per year		63	31	126
Total One-time Costs (millions)		**$1.41**	**$0.40**	**$4.02**
Total Recurring Costs (millions)		**$24.66**	**$1.94**	**$124.01**

We note that on February 2, 2024, FDA issued a final rule amending the device QS regulation, part 820, to align more closely with international consensus standards for devices (87 FR 10119). Specifically, FDA withdrew the majority of the current requirements in part 820 and instead incorporated by reference the 2016 edition of the International Organization for Standardization (ISO) 13485, Medical devices – Quality management systems for regulatory purposes, in part 820. As stated in that rule, the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the current part 820, providing a similar level of assurance in a firm's quality management system, and FDA intends for the phaseout policy to apply with respect to the regulations promulgated through that rulemaking.

The amended QS requirements will take effect on February 2, 2026, before the beginning of Stage 3. Upon the start of Stage 3, or if the laboratory complies with QS requirements prior to the start of Stage 3, FDA expects compliance with the QS requirements that are in effect at that time.[69] For further information on the QS requirements established pursuant to the amendments to the QS regulation, please refer to 89 FR 7496. Notably, the requirements relating to design controls, purchasing controls, acceptance activities, CAPA, and

[69] As noted in the preamble, FDA intends to phase out the general enforcement discretion approach with respect to requirements under 21 CFR 820.198 (complaint files) during stage 1 of the phaseout policy. However, upon the start of stage 1, and prior to the effective date of the amended QS regulation, FDA intends to exercise enforcement discretion and generally not enforce requirements under 21 CFR 820.198 for laboratories that are in compliance with Subclause 8.2.2 of ISO 13485. Following the effective date of the amended QS regulation (February 2, 2026), laboratories must comply with the QS requirements that are in effect at that time.

records requirements are set forth in the following ISO 13485 clauses as modified by the regulatory text for part 820:

- Clause 4. Quality Management System, Subclause 4.2.5;
- Clause 6. Resource Management;
- Clause 7. Product Realization, Subclause 7.1, Subclause 7.3, Subclause 7.4, and Subclause 7.4.3; and
- Clause 8. Measurement, Analysis, & Improvement, Subclause 8.2.2, Subclause 8.2.5, Subclause 8.2.6, and Subclause 8.3.

To the extent amended QS requirements are in effect, we do not expect the total costs for compliance with QS requirements in Stage 3 to substantially change (89 FR 7496, February 2, 2024).

4. Costs Under Stages 4 and 5

Beginning 3½ years after the publication of this final rule, FDA will expect laboratories to comply with premarket review requirements for high-risk IVDs offered as LDTs (21 U.S.C. 360e and 21 CFR part 814). Laboratories will face costs of preparing and submitting premarket approval (PMA) applications and PMA supplements as well as greater annual reporting burdens associated with premarket approval. FDA will also face additional costs of reviewing the applications. We quantify these costs in the following sections.

Additionally, moderate risk IVDs offered as LDTs (IVDs that may be eligible for classification into class II) and low risk IVDs offered as LDTs (IVDs that may be eligible for classification into class I) that require a premarket submission will be expected to comply with 510(k) requirements or De Novo requirements beginning 4 years after the publication of the

phaseout policy. Under this stage, we anticipate costs associated with preparing and submitting 510(k) premarket notifications or De Novo classification requests, and FDA review costs.

FDA generally intends to continue to exercise enforcement discretion with respect to premarket review for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in the preamble. FDA also generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs that receive approval through NYS CLEP. In addition, FDA generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system.

a. Number of Premarket Submissions

Due to the variations in the size of laboratories, business models, and types of IVDs, there is no comprehensive database or repository from which we can definitively calculate the number of IVDs offered as LDTs currently available or the rate at which new IVDs offered as LDTs are introduced. Likewise, there is insufficient data to definitively determine what percentage of IVDs offered as LDTs are likely to be in each class of devices. We rely on New York State Department of Health internal data to estimate the number of affected IVDs offered as LDTs (see section II.D.1 and Table 2).

As discussed in section II.D.1, we assume one laboratory offers 67 IVDs as LDTs and will offer 6 new IVDs as LDTs per year. Of the 67 IVDs as LDTs currently offered per laboratory, we assume that, on average, two will be modified in such a way as to require premarket review per year until they all are FDA authorized. As mentioned above, FDA

generally intends to exercise enforcement discretion with respect to premarket review requirements for LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the health care system. We therefore exclude the number of LDTs from high complexity laboratories integrated within healthcare systems that are likely to be for such unmet needs. We also exclude premarket reviews for LDTs that receive approval through NYS CLEP. In addition, on January 31, 2024, FDA announced its intent to initiate the reclassification process for most IVDs that are currently class III into class II and, therefore, considered the impact of this reclassification process on our estimates of premarket submissions, reducing the number of expected PMAs and increasing the number of expected De Novos and 510(k)s. We explain details of the calculations in appendix A and Table 29.

Because FDA generally intends to exercise enforcement discretion with respect to premarket review for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of this rule and that are not modified, or that are modified as described in the preamble, we only include costs from modified and new IVDs offered as LDTs under Stages 4 and 5.

Table 29. Number of Premarket Submissions Under Stage 4 and Stage 5

	Primary	Low	High
PMA	101	51	203
PMA supplements	31	15	61
510(k) Total	2,179	1,090	4,359
510(k) with method comparison study	1,286	643	2,572
510(k) with moderately complex clinical study	894	447	1,787
De Novo	267	134	534
Total number of new premarket submissions per year for affected tests	**2,578**	**1,289**	**5,157**

Notes: The numbers of tests include currently marketed tests that would be modified per year and new tests from both affected labs and new labs entering the market per year.

b. PMA, 510(k), and De Novo requirements

In estimating the costs of compliance for laboratories, we use estimates for the 510(k) and the premarket approval processes derived by Eastern Research Group (ERG) (Ref. [61]) [70]. The estimates by ERG present the representative costs of regulatory-related activities based on semi-structured discussions with project consultants and other information and knowledge about the development process.[71]

Devices subject to premarket approval typically require premarket and post-market procedures that are not typically associated with 510(k) clearance, such as premarket manufacturing site and clinical site inspections and annual report submissions. In addition, the requirements relating to submissions for device modifications are generally different for devices that have received PMAs as compared with other devices. For example, supplements must be approved, such as for the use of a different facility or establishment to manufacture, process, or package the device. We have excluded costs that would already be part of compliance with the QS requirements under Stage 3, including costs of developing design controls, acquiring GMP-compliant manufacture capability, and developing a risk management system.

To estimate cost for submission and preparation of the PMA, IVDs are broken out by complexity of the clinical trial supporting IVD safety and effectiveness due to the different costs. We use the ERG estimates of the PMAs with complex clinical trials for lower bound estimates (Ref. [61]). For upper bound estimates, we use the ERG estimates of the PMAs with complex, extensive clinical trials. We updated the ERG estimates to account for inflation. We expect that most of the PMAs will involve complex clinical trials. We assume that of the

[70] Another study by ERG used the same source for an analytical framework for examining the value of antibacterial products: https://aspe.hhs.gov/reports/analytical-framework-examining-value-antibacterial-products-0.
[71] We may under- or over-estimate the costs of premarket preparation since the estimates by ERG are not specific to IVDs. We have revised some of the estimates based on FDA professional judgement and historical knowledge.

PMAs, 95% are complex clinical trials and 5% are complex, extensive clinical trials. We take 95% of the low and 5% of the high estimates to calculate primary estimates. The total cost of submission and preparation per PMA is estimated to range from $4.10 million to $9.29 million, with a primary estimate of $4.36 million. Multiplying the estimates by the numbers of new IVDs per year and IVDs from new entities per year that are subject to premarket approval, excluding those that would be under enforcement discretion policies, we expect recurring cost of submission and preparation for PMAs to range from $207.60 million to $1,881.11 million, with a primary estimate of $441.47 million.

PMA holders are also subject to annual reporting requirements, which impose preparation costs on PMA holders and review costs on FDA. We use a prior estimate from the Microbiology Devices; Reclassification of Nucleic Acid-Based Systems for *Mycobacterium tuberculosis* complex final regulatory impact analysis (Ref. [62]) to estimate the recurring preparation cost.[72] The current estimate after adjustment for inflation is $11,798 per PMA. Multiplying the estimates by the numbers of PMA submissions per year, we expect total recurring costs of PMA annual reporting requirements to range from $0.60 million to $2.39 million, with a primary estimate of $1.19 million.

Overall, we estimate the total recurring costs to industry of PMA requirements in Stage 4 to range between $208.20 million and $1,883.50 million, with a primary estimate of $442.67 million. See Table 30.

Table 30. Costs to Industry of Premarket Approval Application

	Primary	Low	High
Cost of Submission and Preparation			

[72] The ICR package of premarket approval of medical devices (OMB control number 0910-0231) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202211-0910-010

Develop necessary SOPs	$39,572	$37,688	$75,376
Hold pre-submission meeting with FDA	$2,513	$2,513	$2,513
Prepare indications for use	$25,125	$25,125	$25,125
Perform clinical trials	$2,832,871	$2,638,150	$6,532,562
Preparing labeling	$25,125	$25,125	$25,125
Pre-approval inspection	$115,576	$115,576	$115,576
Prepare regulatory submission	$1,319,075	$1,256,262	$2,512,524
Subtotal cost per submission	*$4,359,857*	*$4,100,439*	*$9,288,800*
No. PMA submissions per year for affected tests	101	51	203
*Recurring Subtotal (millions)**	*$441.47*	*$207.60*	*$1,881.11*
Recurring Annual			
Annual Report preparation for existing PMAs	$11,798	$11,798	$11,798
No. PMA submissions per year for affected tests	101	51	203
*Recurring Subtotal (millions)**	*$1.19*	*$0.60*	*$2.39*
Total Recurring Costs (millions)	**$442.67**	**$208.20**	**$1,883.50**

Notes:
Unless otherwise specified, line-item estimates are inflation-adjusted estimates from Eastern Research Group, Inc. 2012: Economic Analysis of CDRH Submission Requirements. Totals may not add due to rounding. The numbers of PMA submissions per year include currently marketed tests that would be modified per year and new tests from both affected entities currently on the market and new entities entering the market per year. Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of Q-submissions and PMAs.
**We calculate subtotals by multiplying subtotal cost per submission by the number of affected IVDs.*

Some IVDs with PMAs might require a PMA supplement under 21 CFR 814.39 when certain modifications are made.[73] There are several types of PMA supplements (see Table 31; each row is a type of PMA supplement). We first estimate the expected number of PMA supplements by supplement type by multiplying the number of expected PMAs by the number of expected PMA supplements per PMA[74] and the share of supplements by supplement type.[75] We also multiply by the Remaining PMA Rate (Table A.4, Column F) to adjust for potential

[73] See the following page for a list of changes that would require a PMA supplement: https://www.fda.gov/medical-devices/premarket-approval-pma/pma-supplements-and-amendments.
[74] As of June 2023, the estimated number of active PMAs for all IVDs is 187 and total number of supplements over 7 years is 928. We divide the total number of supplements by the number of active PMAs and 7 years to calculate the number of PMA supplement per active PMA per year, which is 0.71 (= 928 supplements / 187 active PMAs / 7 years). We assume that the same rates for IVDs overall will apply to IVDs offered as LDTs.
[75] We use the FDA internal information on the total number of supplement submissions received by FDA from 2017 to 2023, as of July 2023.

reclassification of Class III IVDs into Class II IVDs. We assume that entities would submit PMA supplements in year 4. See Table 31 for the expected number of annual PMA supplements.

Next, to estimate the total costs to industry of PMA supplement preparation, we multiply the number of PMA supplements by an estimated full-time equivalent (FTE) cost[76] associated with each supplement type and the cost of preparing a PMA from the previous section. This approach assumes the cost of preparing a PMA supplement for a laboratory is proportional to the FTE required for FDA to review the supplement type. Overall, we estimate the total recurring costs to industry of PMA supplements to range from $6.28 million to $56.89 million, with a primary estimate of $13.35 million. See Table 32.

Table 31. Number of PMA Supplements by Submission Type

Submission Type	Cumulative share of supplements by type	Primary	Low	High
135 Review Track	0.053	2	1	5
Normal 180-day track	0.205	5	3	11
Normal 180-day track - No user fee	0.128	4	2	7
Panel-Track	0.067	2	1	4
Real-Time Process	0.374	14	7	28
Special CBE	0.095	4	2	7

Table 32. Costs to Industry of PMA Supplements

Submission Type	Adjusted FTE weights over PMA	Primary	Low	High
135 Review Track	0.033	$0.42	$0.20	$1.79
Normal 180-day track	0.033	$0.98	$0.46	$4.18
Normal 180-day track - No user fee	0.033	$0.67	$0.32	$2.88
Panel Track	1.000	$9.85	$4.63	$41.98
Real Time Process	0.010	$0.79	$0.37	$3.35
Special CBE	0.033	$0.64	$0.30	$2.71
Total Recurring Costs (millions)		**$13.35**	**$6.28**	**$56.89**

Note: Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of PMA supplements.

[76] This cost reflects hours spent in CDRH substantive review of devices, required to determine whether they meet the standard to be approved. It does not include some of the steps required to complete review of a submission, such as management or time spent on such reviews by staff outside CDRH.

Similar to the PMA, we use the ERG estimates of the 510(k) process to estimate the one-time submission and preparation cost of 510(k)s, adjusting for inflation.[77] We use the ERG estimates of 510(k) with small or simple clinical trials for 510(k) submissions with method comparison studies (see Table 33) (Ref. [61]). We use the ERG estimates of 510(k) with moderately complex clinical trials for 510(k) submissions with moderately complex clinical studies (see Table 34).[78]

For any 510(k) submission (or De Novo request[79]), we expect it will take one operations specialist manager, working at a wage of $66.83 ($133.66 fully loaded), 1 to 2 hours (with a primary estimate of 1.5 hours) to identify a predicate device (or determine that no predicate device exists, in the case of a De Novo). The other one-time submission and preparation costs are derived from the ERG estimates. The total cost of submission and preparation per 510(k) with method comparison studies is estimated to range from $215,457 to $279,157, with a primary estimate of $247,307.

FDA also anticipates that laboratories may seek to utilize FDA's 510(k) Third Party Review Program. Multiple Third Party Review Organizations (3P510k Review Organizations) are accredited to conduct reviews of 510(k) submissions for certain IVDs. Manufacturers who submit to 3P510k Review Organizations pay the 3P510k Review Organization but do not pay FDA user fees for those submissions. Each 3P510k Review Organizations sets their own rates, which are generally comparable to FDA user fees. Due to lack of data, we assume that

[77] The ICR package of premarket notification submission 510(k) (OMB control number 0910-0120) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202308-0910-018
The ICR package of De Novo classification process (OMB control number 0910-0844) is available at: https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202111-0910-009

[78] Distinctions of the estimates used in Table 33 and Table 34 are based on the type of study supporting clinical validation of these tests due to differing costs.

[79] In the absence of more detailed information on De Novo costs, we extrapolate 510(k) costs to estimate De Novo costs.

laboratories will pay the same amount of FDA user fees to 3P510k Review Organizations. FDA assumes that at least 50% of the IVDs offered as LDTs being submitted for 510(k) review will be reviewed under the 510(k) Third Party Review Program.

Multiplying by the numbers of modified and new IVDs per year and IVDs from new entities that are subject to 510(k) with method comparison studies, excluding those that would be under enforcement discretion policies per year yields the recurring submission and preparation costs for 510(k)s with method comparison studies is estimated between $142.10 million and $732.21 million, with a primary estimate of $325.15 million. See Table 33.

Table 33. Costs to Industry of 510(k)s (Method Comparison Study)

	Primary	Low	High
Cost of Submission and Preparation			
Identify predicate device			
Hours	1.5	1	2
Wage	$133.66	$133.66	$133.66
Develop necessary SOPs	$37,688	$37,688	$37,688
Hold pre-submission meeting with FDA	$2,136	$1,759	$2,513
Prepare indications for use	$25,125	$25,125	$25,125
Perform method comparison	$62,813	$62,813	$62,813
Preparing labeling	$25,125	$25,125	$25,125
Prepare regulatory submission	$94,220	$62,813	$125,626
Subtotal cost per submission	*$247,307*	*$215,457*	*$279,157*
No. 510(k) submissions with method comparison study per year for affected tests	1,286	643	2,572
Subtotal (millions)	*$317.98*	*$138.52*	*$717.87*
Fees to 3P510k Review Organizations			
MDUFA Review Fee (Adjusted fee for small entities)	$21,760 ($5,440)	$21,760 ($5,440)	$21,760 ($5,440)
IVDs Affected, non-small*	225	113	450
IVDs affected, small*	418	209	836
Subtotal (millions)	*$7.17*	*$3.58*	*$14.34*
Total Recurring Costs (millions)*	**$325.15**	**$142.10**	**$732.21**

Notes:
Unless otherwise specified, line-item estimates are inflation-adjusted estimates from Eastern Research Group, Inc. 2012: Economic Analysis of CDRH Submission Requirements. Totals may not add due to rounding. The numbers of 510(k) submissions per year include currently marketed tests that would be modified and new tests from both affected entities currently on the market and new entities

entering the market per year. Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of Q-submissions and 510(k) submissions.
**We calculate subtotals by multiplying the subtotal cost per submission by the number of affected IVDs.*

Table 34 presents costs of 510(k) submissions with a moderately complex clinical study. We calculate the costs using the exact same methods as in Table 33. The estimated subtotal cost of submission and preparation per submission ranges from $466,709 to $530,410, with a primary estimate of $498,560. Multiplying the estimates by the numbers of modified and new IVDs per year and IVDs from new entities per year that are subject to 510(k) with moderately complex clinical studies, excluding those that would be under enforcement discretion policies, we expect recurring submission and preparation cost to range from $211.00 million to $957.82 million, with a primary estimate of $450.45 million.

Table 34. Costs to Industry of 510(k)s (Moderately Complex Clinical Study)

	Primary	Low	High
Cost of Submission and Preparation			
Identify predicate device			
Hours	1.5	1	2
Wage	$133.66	$133.66	$133.66
Develop necessary SOPs	$37,688	$37,688	$37,688
Hold pre-submission meeting with FDA	$2,136	$1,759	$2,513
Prepare indications for use	$25,125	$25,125	$25,125
Perform clinical study	$314,065	$314,065	$314,065
Preparing labeling	$25,125	$25,125	$25,125
Prepare regulatory submission	$94,220	$62,813	$125,626
Subtotal cost per submission	*$498,560*	*$466,709*	*$530,410*
No. 510(k) submissions with moderately complex clinical study per year	894	447	1,787
Subtotal (millions)	*$445.47*	*$208.51*	*$947.86*
Fees to 3P510k Review Organizations			
MDUFA Review (Adjusted fee for small entities)	$21,760 ($5,440)	$21,760 ($5,440)	$21,760 ($5,440)
IVDs Affected, non-small*	156	78	313
IVDs affected, small*	290	145	581

Subtotal (millions)	*$4.98*	*$2.49*	*$9.96*
Total Recurring Costs (millions)*	**$450.45**	**$211.00**	**$957.82**

Notes:
Unless otherwise specified, line-item estimates are inflation-adjusted estimates from Eastern Research Group, Inc. 2012: Economic Analysis of CDRH Submission Requirements. Totals may not add due to rounding. The numbers of 510(k) submissions per year include currently marketed tests that would be modified and new tests from both affected entities currently on the market and new entities entering the market per year. Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of Q-submissions and 510(k) submissions.
**We calculate subtotals by multiplying subtotal cost per submission by the number of affected IVDs.*

Table 35 shows costs of a De Novo classification request. We use the ERG estimates of 510(k) with moderately complex clinical trial for upper bound and use the ERG estimates of 510(k) with a method comparison study for lower bound estimates (Ref. [61]).[80] We assume that most De Novo requests would have data from clinical trials. We take 99% of the high and 1% of the low estimates to calculate primary estimates. We calculate costs of De Novo classification requests using the exact same methods as in Table 34. The estimated subtotal cost of submission and preparation per submission ranges from $216,211 to $530,410, with a primary estimate of $527,202. Multiplying the estimates by the numbers of modified and new IVDs per year and IVDs from new entities per year that are subject to De Novo, excluding those that would be under enforcement discretion policies, we expect recurring submission and preparation cost to range from $28.88 million to $283.39 million, with a primary estimate of $140.84 million.

Table 35. Costs to Industry of De Novo Classification Request

	Primary	Low	High
Cost of Submission and Preparation			
Determine that no predicate devices exist			
Hours	1.50	1.00	2.00
Wage	$133.66	$133.66	$133.66
Develop necessary SOPs	$37,688	$37,688	$37,688
Hold pre-submission meeting with FDA	$2,513	$2,513	$2,513

[80] In the absence of more detailed information on De Novo costs, we extrapolate 510(k) costs to estimate De Novo costs, noting however that De Novo costs are likely higher than 510(k) costs.

Prepare indications for use	$25,125	$25,125	$25,125
Perform method comparison or clinical study	$311,553	$62,813	$314,065
Preparing labeling	$25,125	$25,125	$25,125
Prepare regulatory submission	$124,998	$62,813	$125,626
Subtotal cost per submission	*$527,202*	*$216,211*	*$530,410*
No. De Novo submissions per year for affected tests	267	134	534
Total Recurring Costs (millions)*	**$140.84**	**$28.88**	**$283.39**

Notes:
Unless otherwise specified, line-item estimates are inflation-adjusted estimates from Eastern Research Group, Inc. 2012: Economic Analysis of CDRH Submission Requirements. Totals may not add due to rounding. The numbers of De Novo submissions per year include currently marketed tests that would be modified and new tests from both affected entities currently on the market and new entities entering the market per year. Total recurring costs does not include costs to FDA. See section II.G for FDA review costs of Q-submissions and De Novo requests.
**We calculate subtotals by multiplying subtotal cost per submission by the number of affected IVDs.*

5. Summary of Costs

Table 36 summarizes our estimates of the one-time and recurring costs by stage of the phaseout policy. These include costs to FDA and costs to industry. We estimate the total one-time costs to range between $11.67 million and $85.30 million, with a primary estimate of $32.45 million. We estimate the total recurring costs to range between $0.72 billion and $4.54 billion, with a primary estimate of $1.65 billion.

Table 36. Total Costs to FDA and Industry (millions 2022$)

		Primary	Low	High
One-time				
Stage 1	Reading and Understanding the Rule	$3.62	$0.81	$12.21
	Medical Device Reporting	$13.21	$5.36	$32.57
	Correction and Removal Reporting	$0.03	$0.01	$0.06
	Complaint Records	$2.11	$0.60	$6.04
Stage 2	Registration and Listing Requirements	$0.41	$0.20	$0.82
	Labeling Requirements	$4.22	$0.54	$14.69
	Investigational Use Requirements	$7.45	$3.73	$14.90
Stage 3	Quality System Requirements	$1.41	$0.40	$4.02
Total One-time Costs (millions)		**$32.45**	**$11.67**	**$85.30**
Recurring Annual				

Stage 1	Reading and Understanding the Rule	$0.29	$0.07	$0.98
	Medical Device Reporting	$82.03	$40.91	$164.55
	Correction and Removal Reporting	$0.15	$0.08	$0.30
	Complaint Records	$0.02	$0.01	$0.05
Stage 2	Registration and Listing Requirements	$0.17	$0.08	$0.34
	Labeling Requirements	$0.34	$0.04	$1.18
	Investigational Use Requirements	$18.02	$9.01	$36.03
Stage 3	Quality System Requirements	$24.66	$1.94	$124.01
Stage 4	Premarket Approval Application	$503.91	$238.82	$2,005.97
	Premarket Approval Application Supplements	$14.76	$6.98	$59.71
Stage 5	510(k) Submission	$825.47	$378.03	$1,789.77
	De Novo Classification Request	$177.50	$47.21	$356.72
Total Recurring Costs (millions)		**$1,647.32**	**$723.18**	**$4,539.61**

Notes: The estimated costs include both costs to industry and FDA. The MDRs review costs for stage 1, the IDEs review costs for stage 2, and the Q-submission and premarket review costs to FDA for stages 4 and 5 are reported in section II.G.

Table 37 presents a summary of the estimated twenty-year stream of costs. We expect that total costs for Stage 1 associated with reading and understanding the rule, medical device reporting, correction and removal reporting, and complaint records would occur in the first year after publication of the final rule. In the first year after publication of the final rule, we estimate total costs to range from $47.85 million to $216.75 million, with a primary estimate of $101.46 million.

We expect that total costs for Stage 2 associated with registration and listing requirements, labeling requirements, and investigational use requirements would occur in the second year after publication of the final rule. In year 2, total costs are estimated to range between $54.67 million to $233.83 million, with a primary estimate of $113.09 million.

In the third year after publication of the final rule, we expect that costs for Stage 3 associated with Quality System requirements except for complaint files would occur. We also expect that half of costs for Stage 4 associated with premarket approval applications would occur

in year 3. Total costs in year 3 are estimated to range between $175.44 million to $1.36 billion, with a primary estimate of $386.41 million.

In subsequent years, we expect that costs for Stages 4 and 5 associated with PMAs, PMA supplements, 510(k) submissions or De Novo classification requests would occur. The recurring cost for year 4 to year 20 is estimated to range between $723.18 million and $4.54 billion, with a primary estimate of $1.65 billion. We estimate the total costs over 20 years to range from $12.57 billion to $78.99 billion, with a primary estimate of $28.61 billion.

The present value of total estimated costs is $20.41 billion at a 3 percent discount rate and $13.64 billion at a 7 percent discount rate over 20 years. The annualized value of costs is $1.37 billion at a 3 percent discount rate and $1.29 billion at a 7 percent discount rate.

Table 37. Twenty-Year Timing of the Costs (millions 2022$)

	Primary	Low	High
Year 1	$101.46	$47.85	$216.75
Year 2	$113.09	$54.67	$233.83
Year 3	$386.41	$175.44	$1,364.29
Year 4-20 (costs for each year)	$1,647.32	$723.18	$4,539.61
Total Costs	$28,605.32	$12,571.97	$78,988.22
Present Value of Total Costs (3%)	$20,407.00	$8,972.00	$56,376.49
Present Value of Total Costs (7%)	$13,637.63	$5,999.18	$37,699.79
Annualized Value of Costs (3%)	**$1,371.67**	**$603.06**	**$3,789.39**
Annualized Value of Costs (7%)	**$1,287.30**	**$566.28**	**$3,558.59**

6. Other Unquantified Costs

Other unquantified social costs associated with the phaseout policy (or consequences of the costs that have been quantified) may include the impact on prices, access to diagnostics if many laboratories exit the market or discontinue offering certain IVDs rather than incur the costs of compliance with FDA requirements, and/or a decrease in the number of new LDTs due to the

increased operation costs of the phaseout policy. There may be instances in which a laboratory may choose to exit the market or discontinue certain IVDs offered as LDTs due to compliance costs. Without information on the revenues or costs of production of IVDs offered as LDTs, however, we are unable to estimate the impact associated with compliance costs on the prevalence of laboratories exiting the market or discontinuing manufacturing of certain IVDs offered as LDTs.

Our analysis in section III (Final small entity analysis) shows that 22% of estimated receipts from IVDs offered as LDTs come from small laboratories (laboratories with annual receipts of less than $41,500,000), which are more likely to reduce operations or exit the market than large laboratories. However, the enforcement discretion policies discussed here -and in the preamble- make it less likely that these smaller laboratories would reduce operations or exit the market.

However, to the extent that some small laboratories might reduce operations or exit the market, it is possible that larger laboratories might take over the production of certain IVDs offered as LDTs, reducing potential impacts on IVD availability. This might concentrate production in a few large laboratories. Under this scenario, prices for certain IVDs offered as LDTs could increase, reducing overall net social benefits. According to economic theory, production concentration under a few laboratories could increase the risk of supply chain contractions, risking shortages for certain IVDs offered as LDTs and therefore affecting prices and access. Although under monopolistic competition, production of more IVDs offered as LDTs in large laboratories could also result in lower production costs due to the economies of scale associated with the operations of such laboratories, they do not produce at the minimum of their average costs curve and may charge prices higher than their marginal cost.

While we recognize that some laboratories might pass the costs of compliance to their customers by raising prices for IVDs offered as LDTs, increased FDA oversight might also help reduce social costs by helping to support coverage and reimbursement determinations and increasing patient accessibility to IVDs for which there is a reasonable assurance of safety and effectiveness.

We also understand that the increased cost to laboratories under the phaseout policy may reduce the amount of revenue a laboratory can invest in creating and/or modifying IVDs offered as LDTs. This could lead to a reduction in the number of new IVDs offered as LDTs and/or modifications of these which incorporate the most up-to-date scientific knowledge. While this may occur, the increased FDA oversight under the phaseout policy may provide more assurance that new and/or modified IVDs offered as LDTs will provide accurate results.

Finally, it is also possible that some laboratories might decide to switch from an IVD offered as an LDT to an FDA-authorized test or to outsource their testing to other laboratories. According to comments, an FDA-authorized test could cost an additional $6 to $35 per test performed. One comment also stated that outsourcing some testing instead of offering IVDs as LDTs could cost them an additional $3,000 to $6,000 per test, while another stated that outsourcing could cost an additional $760,000 annually. An unknown number of laboratories may pursue outsourcing their testing needs or switching to use of an FDA-authorized test rather than introducing a new test that does not fall within an enforcement discretion policy in the phaseout policy. However, we assume that the cost of switching to an FDA-authorized test when available, would cost less than the cost of submitting a premarket submission. We assume that a laboratory would switch to FDA-authorized tests or outsource their testing needs only if submitting a premarket submission was more costly than either of these alternatives. Either way,

the decision would be a private decision made according to their business plan. To the extent that any number of laboratories switch to any number of FDA-authorized tests, or outsource their testing needs, our estimated costs for submitting a PMA or a 510(k) would be overestimated.

G. Budgetary Impacts

In addition to the cost to industry of preparing and submitting various submissions to FDA, including MDRs, IDEs, Q-submissions, PMAs, PMA supplements, 510(k)s, and De Novo requests, there would be incremental review costs for FDA to review these additional submissions. FDA is excluding from new review costs LDTs that are expected to be reviewed by NYS CLEP. For LDTs approved by NYS CLEP, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements. As discussed in appendix A, we estimate that 12.1% (ranging from 6.1% to 24%) of new submissions for IVDs offered as LDTs would not experience new review costs for FDA as a result of FDA's general enforcement discretion policy with respect to the premarket review requirements for LDTs approved by NYS CLEP.

As mentioned in section II.F.4, FDA assumes that at least 50% of the IVDs offered as LDTs being submitted for 510(k) review will be reviewed under the 510(k) Third Party Review Program. Manufacturers who submit to 3P510k Review Organizations pay the 3P510k Review Organization but do not pay FDA user fees for those submissions. Under the MDUFA V agreement, FDA is currently working to enhance the program with the objective of eliminating routine re-review by FDA of third-party reviews.

To estimate the review costs for FDA, we first use average costs per-page based on premarket submission type used in a prior estimate from the Microbiology Devices;

Reclassification of Nucleic Acid-Based Systems for *Mycobacterium tuberculosis* complex final regulatory impact analysis (Ref. [62]). The current estimate after adjustment for inflation is $864,057 per PMA and $20,565 per 510(k) (or per De Novo).[81] We also use labor costs from estimated FTEs for FDA review of different submission types, including MDRs, Q-submissions, IDEs, and premarket submissions.[82] The 3-year average cost of all personnel compensation and benefits paid per FTE at FDA is $315,403 (Ref. [63]). We then multiply this by the estimated FTEs by submission type to estimate the review cost per submission. We use an average of the two estimates for the premarket review cost per submission (we only use the FTEs information for the MDR review cost per listing, IDE cost per submission, and Q-submission cost per submission).

We expect MDR review cost would occur in Stage 1. Multiplying the MDR review cost per listing by the number of MDR submissions yields a total one-time review cost of MDRs between $0.22 million and $0.88 million, with a primary estimate of $0.44 million. Multiplying the review cost per listing by the number of MDR submissions per year yields a total recurring review cost of MDRs between $0.03 million and $0.11 million, with a primary estimate of $0.06 million.

Under stage 2, we expect IDE review cost would incur in year 2. Multiplying the IDE review cost per listing by the number of IDE submissions yields a total one-time review costs of IDEs between $1.16 million and $4.65 million, with a primary estimate of $2.32 million.

[81] We extrapolate 510(k) costs to estimate De Novo costs, noting however that De Novo costs are likely higher than 510(k) costs. However, in the absence of more detailed information, we sometimes rely on such extrapolations to arrive at estimates due to uncertainty.

[82] This cost reflects hours spent in CDRH substantive review of devices, required to determine whether they meet the standard to be approved, cleared, or granted marketing authorization. It does not include some of the steps required to complete review of a submission, such as management or time spent on such reviews by staff outside CDRH.

The estimated recurring review cost of IDEs range from $2.81 million and $11.24 million, with a primary estimate of $5.62 million.

We expect review costs of Q-submission, PMA, 510(k), and De Novo submissions would incur under stages 4 and 5. To estimate the review cost of Q-submissions, we calculate the number of modified and new IVDs per year subject to premarket review by adding the number of PMA, 510(k), and De Novo submissions.[83] Multiplying the review cost per Q-submission by the number of new premarket submissions per year yields a total recurring review cost of Q-submissions between $18.63 million and $74.50 million, with a primary estimate of $37.25 million.

The total recurring review cost of PMAs is estimated to range between $29.33 million to $117.30 million, with a primary estimate of $58.65 million. The total recurring review cost of PMA supplements is estimated to range between $0.71 million and $2.82 million, with a primary estimate of $1.41 million. The total recurring review cost of 510(k)s is estimated to range from $11.02 million to $44.06 million, with a primary estimate of $22.03 million. The recurring review cost of De Novo classification requests is estimated to range from $14.92 million to $59.67 million, with a primary estimate of $29.84 million.

Overall, we estimate the total one-time FDA review costs to range between $1.38 million and $5.53 million, with a primary estimate of $2.77 million. We estimate the total recurring FDA review costs to range between $77.43 million and $309.72 million, with a primary estimate of $154.86 million. See Table 38.[84]

[83] Our estimates of review costs of Q-submissions are uncertain as we assume every premarket submission will have a Q-submission, which is unlikely, and we do not account for the fact that some premarket submissions have multiple Q-submissions or that we receive some Q-submissions that are not tied to a premarket submission. Further, we do not account for the likelihood of receiving Q-submissions prior to Stage 3 as laboratories prepare in advance for premarket submissions.

[84] The costs could be spread over time depending on the time of submission and review.

Table 38. FDA Review Costs by Submission Type

		Primary	Low	High
MDR	FDA review costs using FTE	$5.58	$5.58	$5.58
	Affected IVDs offered as LDTs on the market	79,114	39,557	158,227
	*Subtotal, one-time (millions)**	*$0.44*	*$0.22*	*$0.88*
	MDR submissions per year for affected tests	10,013	5,007	20,026
	*Subtotal, recurring (millions)**	*$0.06*	*$0.03*	*$0.11*
IDE	FDA review costs using FTE	$21,763	$21,763	$21,763
	Affected IVDs offered as LDTs currently on the market	107	53	214
	*Subtotal, one-time (millions)**	*$2.32*	*$1.16*	*$4.65*
	New IDE submissions per year for affected tests	258	129	516
	*Subtotal, recurring (millions)**	*$5.62*	*$2.81*	*$11.24*
Q-submission	FDA review costs using FTE	$25,548	$25,548	$25,548
	Premarket submissions per year (PMAs, 510(k)s, and De Novos) for affected tests	1,454	727	2,908
	*Subtotal, recurring (millions)**	*$37.14*	*$18.57*	*$74.28*
PMA	FDA review costs using page numbers	$864,057	$864,057	$864,057
	FDA review costs using FTE	$294,429	$294,429	$294,429
	Average FDA review costs	*$579,243*	*$579,243*	*$579,243*
	PMA Submissions per year for affected tests	101	51	203
	*Subtotal, recurring (millions)**	*$58.65*	*$29.33*	*$117.30*
PMA Supplements	*Average FDA review costs*	$110,319	$110,319	$110,319
	Supplements per year for affected tests	31	15	61
	*Subtotal, recurring (millions)***	*$1.41*	*$0.71*	*$2.82*
510(k)	FDA review costs using page numbers	$20,565	$20,565	$20,565
	FDA review costs using FTE	$19,870	$19,870	$19,870
	Average FDA review costs	*$20,218*	*$20,218*	*$20,218*
	510(k) submissions per year for affected tests	1,090	545	2,179
	*Subtotal, recurring (millions)**	*$22.03*	*$11.02*	*$44.06*
De Novo	FDA review costs using page numbers	$20,565	$20,565	$20,565

	FDA review costs using FTE	$202,804	$202,804	$202,804
	Average FDA review costs	*$111,685*	*$111,685*	*$111,685*
	De Novo submissions per year for affected tests	267	134	534
	*Subtotal, recurring (millions)**	*$29.84*	*$14.92*	*$59.67*
Total one-time costs (millions)		**$2.77**	**$1.38**	**$5.53**
Total recurring costs (millions)		**$154.86**	**$77.43**	**$309.72**

Notes: The number of submissions per year include currently marketed tests that would be modified and new tests from both affected entities currently on the market and new entities entering the market per year. The number of premarket submissions per year for Q-submission review costs include all premarket submission types (PMA, 510(k), and De Novo). Totals may not add due to rounding.
**We calculate subtotals by multiplying average FDA review costs by the number of submissions per year.*
***We multiply the average FDA review cost per PMA by the FTE weights to calculate the review cost per PMA supplement.*

H. Transfers

With this phaseout policy, laboratories will pay fees to FDA for establishment registration, premarket submissions (where applicable), and periodic reporting for IVDs with a PMA. While these fees are paid by laboratories, they are revenue for FDA. The approach to estimating fee effects is distinct from the approaches for either benefits or costs, so they will be presented as transfers. Another perspective on the user fees is that they indicate industry bearing costs that are otherwise more simplistically presented as being experienced by FDA; hypothetically, adding the user fee estimates into the cost accounting would double-count effects on net social benefits.[85]

See Table 39 for the estimated transfers associated with the phaseout policy. All anticipated fees are public information published by FDA.[86] Each laboratory is expected to pay an annual registration fee, at a cost of $7,653 per laboratory. Laboratories will also pay for submission of a report annually to FDA for each IVD that has received premarket approval,

[85] Net social benefits are the total benefits minus the total costs to society (industry, consumers, government, etc.). A transfer is a type of change where one member of society bears a cost that would simultaneously be a benefit to another member of society, resulting in a net effect of zero on social benefits. Industry and the FDA are both members of society.
[86] We cite FY24 fees; the fees are updated every summer for the upcoming fiscal year. https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa

which costs $16,925 per report. Laboratories will pay $483,560 to FDA for each PMA they submit. For PMA supplements, they will pay $72,534 for each 180-day supplement, $386,848 for each panel-track supplement, and $33,849 for each real-time supplement they submit. They will pay $21,760 for each 510(k) they submit and $145,068 for each De Novo request they submit.

As mentioned in sections II.F.4 and II.G, we assume that at least 50% of the IVDs offered as LDTs being submitted for 510(k) review will be reviewed under the 510(k) Third Party Review Program. We consider the fees paying to 3P510k Review Organizations as costs to industry, as described in section II.F.4 (see Table 33 and Table 34).

Small businesses that have gross receipts or sales of $100 million or less for the most recent tax year (including their affiliates) are eligible to pay a reduced fee for certain submissions, including:

- 510(k) submissions ($5,440 per submission),
- De Novo requests ($36,267 per submission),
- PMAs ($120,890 per submission),
- PMA supplements ($18,134 for each 180-day supplement, $96,712 for each panel-track supplement, and $8,462 for each real-time supplement), and
- PMA annual reports ($4,231 per submission).

Small businesses with sales of $30 million or less are eligible to have the fee waived on their first PMA.

We assume 40 to 90 percent of the laboratories would have gross receipts or sales of $100 million or less, and we use 65 percent (average of 40 and 90 percent) to estimate the number of small businesses IVDs. Multiplying these fees by the relevant number of laboratories

and IVDs, we expect total annual transfers to range from $34.13 million to $137.09 million, with a primary estimate of $68.54 million.

Table 39. Transfers

			Primary	Low	High
Recurring Annual	Registration Annual Fee	Fee	$7,653	$7,653	$7,653
		Entities affected	1,275	638	2,551
		Subtotal (millions)	*$9.76*	*$4.88*	*$19.52*
	Annual reporting on PMA	Fee (Adjusted fee for small entities)	$16,925 ($4,231)	$16,925 ($0)	$16,925 ($4,231)
		IVDs affected, non-small*	35	18	71
		IVDs affected, small*	66	33	132
		Subtotal (millions)	*$0.88*	*$0.30*	*$1.76*
One-time /Annual	PMA	MDUFA Review (Adjusted fee for small entities)	$483,560 ($120,890)	$483,560 ($120,890)	$483,560 ($120,890)
		IVDs affected, non-small*	35	18	71
		IVDs affected, small*	66	33	132
		Subtotal (millions)	*$25.09*	*$12.55*	*$50.19*
	PMA Supplements –180-day track	MDUFA Review (Adjusted fee for small entities)	$72,534 ($18,134)	$72,534 ($18,134)	$72,534 ($18,134)
		IVDs affected, non-small*	2	1	4
		IVDs affected, small*	4	2	7
		Subtotal (millions)	*$0.20*	*$0.10*	*$0.40*
	PMA Supplements – Panel-track	MDUFA Review (Adjusted fee for small entities)	$386,848 ($96,712)	$386,848 ($96,712)	$386,848 ($96,712)
		IVDs affected, non-small*	1	0	1
		IVDs affected, small*	1	1	2
		Subtotal (millions)	*$0.36*	*$0.18*	*$0.71*
	PMA Supplements – Real-Time	MDUFA Review (Adjusted fee for small entities)	$33,849 ($8,462)	$33,849 ($8,462)	$33,849 ($8,462)
		IVDs affected, non-small*	5	2	10
		IVDs affected, small*	9	4	18
		Subtotal (millions)	*$0.24*	*$0.12*	*$0.48*
	510(k)	MDUFA Review (Adjusted fee for small entities)	$21,760 ($5,440)	$21,760 ($5,440)	$21,760 ($5,440)
		IVDs Affected, non-small*	381	191	763
		IVDs affected, small*	708	354	1,417
		Subtotal (millions)	*$12.15*	*$6.08*	*$24.30*
	De Novo	MDUFA Review (Adjusted fee for small entities)	$145,068 ($36,267)	$145,068 ($36,267)	$145,068 ($36,267)

		IVDs affected, non-small*	94	47	187
		IVDs affected, small*	174	87	347
		Subtotal (millions)	*$19.86*	*$9.93*	*$39.72*
Total Recurring Transfers (millions)			**$68.54**	**$34.13**	**$137.09**

**The numbers of tests include currently marketed tests that would be modified in such a way as to require premarket review as well as new tests subject to premarket review from existing and new entities per year.*

I. Stream of Benefits, Costs, and Transfers

We describe how we estimate the benefits, costs, and transfers in sections II.E, II.F, II.G and II.H. See Table 40 for a summary of the timing of expected benefits, costs, and transfers over a twenty-year time frame, in millions of 2022 U.S. dollars. Only primary estimates are presented. For each year, we present the undiscounted benefits, costs to industry, costs to FDA, and transfers.

Table 40. Undiscounted Twenty-year Flow of Benefits, Costs, and Transfers (millions 2022 USD)

Year	Benefits		Costs to Industry	Costs to FDA	Transfers
	VSLY based on 3% discounting	VSLY based on 7% discounting			
1	$0.00	$0.00	$101	$0	$0
2	$0.00	$0.00	$105	$8	$10
3	$3,111	$2,725	$332	$54	$23
4	$3,151	$2,760	$1,492	$155	$68
5	$4,420	$3,871	$1,492	$155	$69
6	$4,613	$4,041	$1,492	$155	$69
7	$4,786	$4,192	$1,492	$155	$69
8	$4,939	$4,326	$1,492	$155	$69
9	$5,075	$4,446	$1,492	$155	$69
10	$5,197	$4,552	$1,492	$155	$69
11	$5,305	$4,647	$1,492	$155	$69
12	$5,403	$4,732	$1,492	$155	$69
13	$5,490	$4,808	$1,492	$155	$69
14	$5,568	$4,877	$1,492	$155	$69
15	$5,638	$4,938	$1,492	$155	$69
16	$5,701	$4,994	$1,492	$155	$69
17	$5,758	$5,044	$1,492	$155	$69
18	$5,810	$5,089	$1,492	$155	$69

19	$5,856	$5,130	$1,492	$155	$69
20	$5,899	$5,167	$1,492	$155	$69

Table 40 shows that for most years in the twenty-year time horizon, FDA review costs are greater than transfers. The total annualized values of FDA review costs, transfers, and the differences are presented in Table 41. These estimates are conducted using our current fiscal year 2024 Medical Device User Fee program (MDUFA) fee structure. We note that user fee payments are only intended to cover a portion of FDA review costs for premarket submissions.

Under the phaseout policy, FDA does not intend to phase out the general enforcement discretion approach for premarket review requirements for high risk IVDs offered as LDTs (Stage 4) before October 1, 2027, or for other IVDs offered as LDTs that require a premarket submission (Stage 5) before April 1, 2028. October 1, 2027, is the start of the next medical device user fee program (i.e., MDUFA VI).[87]

Table 41. Summary of FDA Review Costs and Transfers (Annualized over 20 years, in millions 2022$)

	Discount rate	Primary	Low	High
FDA Review Costs	3%	$129.30	$64.65	$258.59
	7%	$121.39	$60.69	$242.77
Transfers	3%	$57.50	$28.65	$115.05
	7%	$40.60	$20.24	$81.27
Difference (=FDA Costs - Transfers)	3%	$71.80	$36.00	$143.54
	7%	$80.78	$40.45	$161.51

[87] Note that under the phaseout policy, FDA intends to phase out the general enforcement discretion approach for establishment registration requirements during the current MDUFA V program, such that user fee payments for establishment registrations (which are distinct from user fee payments for premarket submissions) will be subject to the current MDUFA V fee structure.

After calculating the expected benefits, costs, and transfers for each year in a twenty-year time horizon, we calculate the present and annualized values using three and seven percent discount rates. See Table 42.

Table 42. Summary of Present and Annualized Values (in millions 2022$)

	Benefits	Costs*	Transfers
Present Value 7%	$37,176.54	$13,637.63	$430.15
Present Value 3%	$64,583.82	$20,407.00	$855.46
Annualized Value 7%	$3,509.20	$1,287.30	$40.60
Annualized Value 3%	$4,341.05	$1,371.67	$57.50

*The estimated costs include both costs to industry and FDA.

J. Analysis of Regulatory Alternatives to the Final Phaseout Policy

We consider four different regulatory alternatives as described below. In our analysis of alternatives, we compare total costs, benefits, and transfers with two options that would be more stringent and one option that would be less stringent. We also consider one alternative of taking no new action. Table 43 summarizes our analysis of the alternatives of the phaseout policy.

Table 43. Annualized Values of Regulatory Alternatives Over a 20 Year Period (in billions 2022$)

	Final Phaseout Policy		Alternative 2		Alternative 3		Alternative 4	
	3%	7%	3%	7%	3%	7%	3%	7%
Total Benefits	$4.34	$3.51	$4.39	$3.57	$3.94	$3.10	$5.14	$4.21
Total Costs	$1.37	$1.29	$1.45	$1.39	$1.20	$1.09	$5.58	$5.83
Net Benefits	$2.97	$2.22	$2.94	$2.18	$2.74	$2.01	-$0.44	-$1.62
Transfers	$0.06	$0.04	$0.06	$0.06	$0.05	$0.03	$0.28	$0.23

Notes: We report primary estimates. There would be no additional costs or benefits under Alternative 1.

1. We treat one alternative of taking no new action as the baseline for determining the costs and benefits of other alternatives. Under this option, there will be no additional costs or benefits relative to the status quo.
2. The second regulatory alternative reduces the phaseout period to three years following the publication date of the final rule:
    - Stage 1: beginning 1 year after the publication date of this final rule, FDA will expect compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files).
    - Stage 2: beginning 2 years after the publication date of this final rule, FDA will expect compliance with requirements not covered during other stages of the phaseout policy, including registration and listing, labeling, investigational use requirements, and QS requirements under part 820 (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1).
    - Stage 3: beginning 3 years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for high-risk IVDs and other premarket review requirements (for moderate-risk and low-risk IVDs that require premarket submissions).

Under this alternative, we assume that one-time and recurring costs of the QS requirements would occur in year 2 and costs of the PMA, 510(k), and De Novo submissions would occur in year 3. The estimated annualized costs of this alternative would be $1.39 billion, which is $99 million higher than the estimated costs associated with the phaseout policy. The estimated annualized transfers of this alternative would be $58 million, which is $17 million higher than the estimated transfers associated with the phaseout policy. The shorter phaseout period would

result in higher annualized benefits because they would begin earlier than under the phaseout policy. The estimated annualized benefits of this alternative would be $3.57 billion, which is $56 million higher than the benefits associated with the phaseout policy. However, a shorter phaseout period means that, among other things, affected laboratories, including small laboratories, would have less time to prepare and it might be less feasible for them to come into compliance.

3. The third alternative extends the phaseout period to ten years for small entities (i.e., laboratories that have their annual receipts and sales less than $100 million) and six years for other entities:
    - Stage 1: beginning 1 year after the publication date of this final rule, FDA will expect compliance with MDR requirements, correction and removal reporting requirements, and QS requirements under § 820.198 (complaint files).
    - Stage 2: beginning 4 years after the publication date of this final rule, FDA will expect compliance with requirements other than MDR, correction and removal reporting, and QS requirements under part 820 (other than requirements under § 820.198 (complaint files), which are already addressed in stage 1).
    - Stage 3: beginning 5 years (7 years for small laboratories) after the publication date of this final rule, FDA will expect compliance with respect to premarket review requirements for high-risk IVDs.
    - Stage 4: beginning 6 years (10 years for small laboratories) after the publication date of this final rule, FDA will expect compliance with respect to premarket review requirements for moderate risk and low risk IVDs that require premarket submissions.

Compared to the final phaseout policy, having a longer phaseout period would reduce the burden on the affected laboratories by shifting costs into the future. Costs for Stage 2 under the

phaseout policy (including compliance with registration and listing, labeling, and investigational use requirements) would occur in year 2, and costs for Stage 3 under the phaseout policy (relating to compliance with QS requirements) would occur in year 3, but we assume that costs for Stage 2 under this alternative (which would include the costs for Stage 2 and Stage 3 under the phaseout policy) would occur in year 4. We assume that costs for Stage 3 under this option would occur in year 5 (year 7 for small entities). We finally assume that costs for Stage 4 under this option would occur in year 6 (year 10 for small entities). The affected laboratories would thus have lower costs under Stages 2 to 4, except that the costs for Stage 1 would still occur in the first year after issuance of the final phaseout policy. The estimated annualized costs of this alternative would be approximately $1.09 billion, which is $202 million less than the estimated costs associated with the phaseout policy. Out of the estimated annualized costs, the estimated annualized costs to FDA would be approximately $96 million under this alternative, which is $25 million less than the estimated FDA review costs with the phaseout policy. In addition, the longer phaseout period for small laboratories would mean that these entities would have more time to prepare premarket submissions, potentially making it more feasible for them to come into compliance. However, this option would also reduce annualized benefits by $411 million because extending the phaseout period to six years (and ten years for small laboratories) will reduce the number of avoided harms from problematic IVDs.

4. In the fourth alternative, we assume the same phaseout policy as proposed in the preamble to the proposed rule. Under this alternative, there would be one-time costs of the QS requirements and premarket review requirements because FDA would be phasing out the general enforcement discretion approach for currently marketed IVDs offered as LDTs under stages 3 through 5.

The affected laboratories would thus have higher total costs. The estimated annualized costs of this alternative would be approximately $5.83 billion, which is $4.55 billion higher than the estimated costs associated with the final phaseout policy. This alternative would also increase annualized transfers by $194 million. Since this alternative does not consider premarket reviews by third parties or NYSDOH, the costs to FDA would be higher than the estimated costs of the final phaseout policy. We estimate that costs to FDA with this alternative would increase by $552 million, from $121 million to $673 million.

The benefits would increase because the number of affected tests under stages 3 through 5 would be higher than under the final phaseout policy. We estimate that the benefits associated with this alternative would be approximately $4.21 billion, which is $703 million higher than the estimated benefits of the final phaseout policy. Table 44 below summarizes primary estimates of the costs by stage of the phaseout policy and alternative 4. The cost reduction of the final phaseout policy compared to this alternative is primarily due changes in stages 3 through 5 due to the enforcement discretion policies. See Table 19 for the impact of the enforcement discretion policies on the benefits.

Table 44. Costs of the Final Phaseout Policy and Alternative 4 (millions 2022$)

		Final Phaseout Policy	Alternative 4
Stage 1	Reading and Understanding the Phaseout Policy	$3.91	$3.91
	Medical Device Reporting	$95.24	$95.24
	Correction and Removal Reporting	$0.18	$0.18
	Complaint Records	$2.13	-
Stage 2	Registration and Listing Requirements	$0.58	$0.58
	Labeling Requirements	$4.55	$4.55
	Investigational Use Requirements	$25.47	$25.47
Stage 3	Quality System Requirements	$26.06	$472.19
Stage 4	Premarket Approval Application	$503.91	$21,589.11
	Premarket Approval Application Supplements	$14.76	$289.24
Stage 5	510(k) Submission	$825.47	$13,746.59

	De Novo Classification Request	$177.50	$2,882.49

Notes: We only report primary estimates. The estimated costs include one-time costs and recurring costs per year. The estimated costs include both costs to industry and FDA.

K. Distributional Effects

Phasing out the general enforcement discretion approach for LDTs might generate benefits and costs that accrue differentially to establishments and segments of society. In this section, we discuss health equity effects for populations on which IVDs offered as LDTs are used. We address differential effects for small entities in section III of this analysis.

As described in section II.E, we expect the phaseout policy to increase the accuracy of laboratory test results, reducing the incidence of patient diagnostic error and resulting in more appropriate treatments and improved health outcomes, among other benefits. While we would not expect the benefits of the phaseout policy – in isolation – to differentially affect certain population segments, existing inequities in healthcare access might result in differential accrual of benefits across the general population. For example, there is evidence of disparities in access to tests (Ref. [64]) which might impact the patient populations that the benefits of the phaseout policy would reach. FDA also recognizes that IVDs offered as LDTs might serve communities in rural, medically underserved areas with disparities in access to diagnostic tests.

However, the benefits of test access depend on the ability of tests to work as intended, and the harms of unsafe or ineffective IVDs offered as LDTs might disproportionately occur among medically underserved patient populations that such tests might aim to reach. Without appropriate oversight, IVDs offered as LDTs might exacerbate health disparities. Research reports higher rates of inaccurate results among underrepresented patient populations, particularly racial and ethnic minorities undergoing genetic tests (Refs. [65, 66, 67, 68, 69]).

Additionally, some IVDs offered as LDTs have not been validated for use in all patient populations who may have the relevant health condition, across ages or ethnicities, meaning that it is unknown how well the test might perform across diverse patient populations expected to use the test, and tests might be less accurate in underrepresented patient populations, which could contribute to health disparities (Ref. [70]).

The role of IVDs offered as LDTs in either ameliorating or exacerbating existing health inequity ultimately depends on the safety and effectiveness of IVDs offered as LDTs, which the phaseout policy is intended to help assure. By increasing its oversight, FDA might better prevent and mitigate harms disproportionately realized among underrepresented, medically underserved populations. As such, the benefits of phasing out the general enforcement discretion approach for LDTs might differentially reach these populations.

When IVDs are subject to increased FDA oversight, FDA will help ensure that information is available pertaining to device safety and effectiveness for specific demographic characteristics if performance differs within the target population, through the enforcement of applicable labeling requirements. In addition, when FDA conducts premarket review of a device, FDA may ask that sponsors provide data for different intended patient populations. With new FDA authorities under the Food and Drug Omnibus Reform Act of 2022 (FDORA), sponsors will generally be required to submit diversity action plans to FDA, including the sponsor's goals for enrollment in device clinical studies, to help improve the generalizability of the results to the intended use population. In contrast, with limited oversight over these IVDs, FDA does not know whether validation studies for these IVDs include diverse patient populations. FDA believes increased oversight for these IVDs will help ensure adequate representation of the intended use

population in validation studies and transparency regarding potential differential performance, helping to advance health equity.

Nonetheless, while phasing out the general enforcement discretion approach for LDTs might help to advance health equity, we have no specific data showing that increased FDA oversight of IVDs offered as LDTs will necessarily reduce health disparities.

As described in section II.F.6, pass-through of costs to provide IVDs offered as LDTs might in turn create additional costs to society. If laboratories pass through the cost of compliance to the costs of IVDs offered as LDTs, test frequency might decrease for areas that rely on IVDs offered as LDTs for easy, rapid access to tests.[88] If laboratories or healthcare facilities respond to increased compliance costs by increasing the prices of IVDs offered as LDTs or reducing the availability of IVDs offered as LDTs, there might thus be an increase in health inequity. Vulnerable populations that rely on IVDs offered as LDTs for diagnosis might have less access to diagnostic tests in general after the implementation of the phaseout policy.

However, in the absence of assurances about the safety and effectiveness of these tests, the value of access is uncertain. We further note that in the event any currently marketed tests for underserved populations are withdrawn from the market due to their inability to meet regulatory requirements, other manufacturers may fill the need with appropriately designed and validated tests.

We do not expect the phaseout policy to result in an increase in health inequity in isolation. Though we do have evidence of existing health inequities in diagnostic tests and clinical trials across sociodemographic populations, we lack the evidence to quantify the effect of the phaseout policy on these existing health inequities, and thus cannot determine whether the

[88] A 2021 Pew Charitable Trusts' survey of laboratory managers found that 'rapid access' and 'patient need' where top reasons why laboratory managers would choose to employ an LDT (Ref. [27]).

phaseout policy will ameliorate or exacerbate health inequity. By increasing oversight over IVDs offered as LDTs, FDA may better prevent and mitigate harm to patients that might result from inaccurate and unreliable tests, including patients in underserved populations.

L. International Effects

While the phaseout policy will generate benefits that accrue to the domestic population, some laboratories that are located outside the United States would be expected to comply with applicable device requirements, as a result of the phaseout of the general enforcement discretion approach for LDTs, if those laboratories offer IVDs as LDTs to patients within the United States. This section estimates the cost of compliance for international laboratories. These costs are not included in section II.F, which only assesses domestic costs.

As of January 2024, there are 74 international laboratories certified under CLIA to perform non-waived testing.[89] Based on available information and professional judgment, we assume that 100% of CLIA-certified international laboratories are performing high complexity testing and have IVDs offered as LDTs. While our historical experience indicates that these laboratories likely offer a smaller number of IVDs offered as LDTs, as they are typically offering more specialized tests, for the cost estimates, we use the same assumption described in section II.D that each laboratory would have 67 IVDs offered as LDTs, and thus we expect 496 (= 74 x 67) international IVDs offered as LDTs to be affected by the phaseout policy. We also assume 592 (74 x (6+2)) modified (an additional 2 annually) and new (an additional 6 annually) international IVDs offered as LDTs to be affected annually, consistent with assumptions in section II.D.

[89] https://qcor.cms.gov/advanced_find_provider.jsp?which=4&backReport=active_CLIA.jsp

We also adjust wages to reflect the fact that international laboratories may not offer the same wages as those in the United States. Specifically, we create a list of the unique countries that appear in our data on the 74 international laboratories, then search the National Bureau of Economic Research (NBER) Occupational Wages around the World (OWW) database for wage information for the relevant countries.[90] The most recent year with complete data is 2007. We observe the average hourly wage rate across all sectors for the relevant countries in U.S. dollars, then divide by the same measure for U.S. wages to get a relative measure of wages as percent deviation from the U.S. hourly wage rate for the same period. We then take the average percent deviation across the relevant countries and find that wages for the relevant international countries are 73% that of U.S. wages for the same time period. We therefore adjust the wages we use in the domestic cost analysis by 0.73 to assess international costs.

Aside from coverage and wage rates, the costs for international laboratories are calculated using the exact same methods as in section II.F. Because there are significantly fewer laboratories and tests, and wages are slightly lower, international costs are much lower than domestic costs of compliance. See Table 45 for a summary of international costs, organized by stage and part of the phaseout policy.

Table 45. International Costs

		Primary	Low	High
One-time				
Stage 1	Reading and Understanding the Rule	$165,541	$74,494	$279,351
	Medical Device Reporting	$612,171	$498,064	$752,796
	Correction and Removal Reporting	$1,850	$1,850	$1,850
	Complaint Records	$96,644	$55,225	$138,062
Stage 2	Registration and Listing Requirements	$18,669	$18,669	$18,669
	Labeling Requirements	$192,916	$49,785	$336,048

[90] https://www.nber.org/research/data/occupational-wages-around-world-oww-database

	Investigational Use Requirements	$466,943	$466,943	$466,943
Stage 3	Quality System Requirements	$96,644	$55,225	$138,062
Total One-time Costs		**$1,651,379**	**$1,220,255**	**$2,131,781**
Recurring Annual				
Stage 1	Medical Device Reporting	$3,707,098	$3,707,090	$3,707,106
	Correction and Removal Reporting	$6,845	$6,845	$6,845
Stage 2	Re-registration	$6,223	$6,223	$6,223
	Investigational Use	$1,129,027	$1,129,027	$1,129,027
Stage 4	Premarket Approval Application	$59,172,917	$56,088,281	$117,781,004
	Premarket Approval Application Supplements	$1,733,605	$1,640,318	$3,506,047
Stage 5	510(k) Submission	$104,382,781	$96,222,502	$112,543,060
	De Novo Classification Request	$20,842,241	$11,086,707	$20,942,297
Total Recurring Costs		$190,980,737	$169,886,993	$259,621,610

See Table 46 for a summary of the expected timing and annualized value of international costs. At a three percent discount rate, we expect the annualized value of international costs to range from $140.29 million to $214.98 million, with a primary estimate of $157.50 million. At a seven percent discount rate, we expect the annualized value of international costs to range from $131.23 million to $201.26 million, with a primary estimate of $147.26 million.

Table 46. Twenty-Year Timing of International Costs (millions 2022$)

	Primary	Low	High
Year 1	$4.59	$4.34	$4.89
Year 2	$5.53	$5.38	$5.67
Year 3	$35.40	$33.77	$65.63
Year 4-20 (costs for each year)	$190.98	$169.89	$259.62
Total Costs of the Phaseout Policy	$3,292.19	$2,931.58	$4,489.76
Present Value of Total Costs (3%)	$2,343.16	$2,087.14	$3,198.30
Present Value of Total Costs (7%)	$1,560.07	$1,390.28	$2,132.20
Annualized Value of Costs (3%)	$157.50	$140.29	$214.98
Annualized Value of Costs (7%)	$147.26	$131.23	$201.26

III. Final Small Entity Analysis

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because most facilities that will be affected by the phaseout of the general enforcement discretion approach for LDTs are defined as small businesses and the phaseout policy is likely to impose a substantial burden on the affected small entities, we find that the phaseout policy will have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document and the final rule, serves as the Final Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

We used detailed data from 2017 Statistics of U.S. Businesses on U.S. 6-digit NAICS detailed employment sizes and revenues to analyze the potential impacts of the phaseout policy on small entities. The Small Business Administration (SBA) considers Medical Laboratories (NAICS code 621511) to be small if their annual receipts are less than $41.5 million.[91] Since not all laboratories in this NAICS code offer IVDs as LDTs, we use the number of affected laboratories and distribute them proportionally across the revenue distribution from the Economic Census to estimate breakdown of the laboratories by revenue size (see Table 47). Of the 1,181 laboratories, 1,085 laboratories (those with less than $41.5 million in annual receipts), or 92 percent of the total, would be small according to the 2023 SBA size standard. We estimate

[91] Small Business Association. Table of Size Standards. March 17, 2023. Available from: https://www.sba.gov/document/support-table-size-standards

that small businesses also manufacture 22% of IVDs offered as LDTs currently on the market.[92] We provide more detail on these estimates in Appendix B.

Table 47. Distribution of Revenues for Laboratories Offering IVDs as LDTs

Receipts Size ($1,000)	Number of Laboratories Under NAICS Code 621511	Number of Laboratories Offering IVDs as LDTs	Number of IVDs offered as LDTs
< $150	438	166	56
$151 - $999	933	327	625
$1000 - $1,999	413	145	754
$2,000 - $3,999	481	169	1,948
$4,000 - $5,999	343	120	3,061
$6,000 - $9,999	146	51	2,150
$10,000 - $14,999	77	27	1,489
$15,000 - $19,999	115	40	3,114
$20,000 - $24,999	79	28	2,920
$25,000 - $29,999	21	7	951
$30,000 - $39,999	43	15	2,270
$40,000 - $49,999	15	5	1,151
$50,000 - $99,999	67	24	5,475
$100,000 +	194	68	63,163
Total	3,365	1,193	89,127
< $41.5 million	3,091	1,097	19,510
Percent Small	92%	92%	22%

B. Description of the Potential Impacts of the Phaseout Policy on Small Entities

We compiled the costs and transfers associated with the phaseout policy and compared them to the estimated share of annual receipts of the laboratories offering IVDs as LDTs. In Table 48, we estimate the total annualized costs per entity at a 7 percent discount rate over 20 years and the costs as a percent of revenue by receipts size. The estimated annualized cost per small entity ranges from $4,395 to $3,045,766 per laboratory, depending on its size

[92] From Table 47 an estimated 17,318 of 79,114 IVDs or 22% offered as LDTs are from small businesses.

classification.[93] As shown in Table 48, the annualized costs per small entity averages $232,618 represent 5.8 percent of receipts for the small laboratories (with annual receipts of less than $41,500,000). Because we don't know how costs would be distributed across entities, we estimate average costs per laboratory by their receipt size categories using the assumption that costs are distributed proportionally to receipts and for this reason costs as a percent of receipts appear to be constant across all receipt size categories.

The extent in which smaller laboratories may be disproportionately impacted by the phaseout of the general enforcement discretion approach for LDTs, is dependent on the number of IVD's offered as LDTs per lab. FDA anticipates that the enforcement discretion policies discussed in the preamble of the final rule will moderate these concerns and help to avoid complete disruption to the test market. As noted in Appendix B-Table 8, the average costs per LDT are smallest for stages 1 through 3 of the phaseout policy representing 10% of costs and up to 59% of affected tests, whereas average costs per LDT for stages 4 and 5 represent 90% of costs affecting 3% of tests. The percentage of tests that may experience costs under stages 4 and 5 will increase as new laboratories and tests enter the market during and after stages 4 and 5, as they will fall within the enforcement discretion policy for currently marketed tests. However, they may still fall within the scope of other enforcement discretion policies described in the preamble to the final rule, including those for unmet needs and LDTs approved by NYS CLEP. However, in the event that a new lab does not fall within the scope of other enforcement discretion policies, costs under stages 4 and 5 could present as a potential barrier to entry in the LDT market for new laboratories. In Table B7 of Appendix B, total costs and transfers of the phaseout policy are estimated to be on average anywhere between about 2.54, 5.8 and 16 percent

[93] The average annualized cost per small entity ranges from $4,395 per laboratory with annual receipts that are less than $150,000 and to $3,045,766 per laboratory with annual receipts between $40 and $49.99 million.

for all entities. We do not have the information about labs to determine how the average estimates are distributed among the firms according to their size categories. Depending on profit margins with respect to revenue, the costs of this rule may be prohibitive for some small labs, making it likely for some small entities in this size category to exit the market, reduce operations, sell the business, be subject to acquisitions by larger firms or not enter the market. If profit margins were too small for many small firms considering the costs, it is possible that selling to large entities, would further cause industry consolidation and contribute to the growth of monopolies in the industry which would hinder competition. As we explained in Comment 17 (small entities), we do not have the information about labs to determine how the average estimates are distributed among the firms according to their size categories. Also, costs would be higher for a lab that has several IVDs offered as LDTs but sells fewer units tests whereas costs would be smaller for labs with only one IVD offered as LDTs selling a large number of unit tests. In the same manner, profit margins could be higher for labs with a smaller number of IVDs offered as LDTs but with high volume unit tests sold, compared to labs with a larger number of IVDs offered as LDTs but with low volume units tests sold.

While we do not have the data on profit margins to properly estimate the number of labs that would be adversely impacted by this rule, we estimate that small laboratories make fewer IVDs offered as LDTs than large firms. We estimate that small labs make up 92 percent of all labs, and that they also hold a 24 percent share of IVDs offered as LDTs. With the low number of IVDs offered as LDTs per small lab, it is more likely that the percent of costs over receipts per lab would be closer to our low average estimate 2.5 percent. Furthermore, for the final rule, as explained in comments 17 and 18, FDA intends to exercise enforcement discretion with respect to premarket review and QS requirements (except for applicable requirements under 21 CFR

820, subpart M (Records)) for currently marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the final rule and that are not modified, or that are modified as described in the preamble and for LDTs developed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system (as described in section V.B.3 of the preamble), we do not expect significant market concentration or market exit to result from the phaseout policy.

Small businesses that have gross receipts or sales of $100 million or less for the most recent tax year (including their affiliates) are eligible to pay a reduced fee for certain submissions, including 510(k) submissions, De Novo classification requests, PMAs, and PMA annual reports.[94] The estimated average recurring transfer for small businesses is $4,069. As seen in Table 48, the percentage of receipts that are additional transfers associated with the phaseout policy are estimated to be 0.10 percent for 166 laboratories (15 percent of the small entities) with their annual receipts less than $150,000.

Table 48. Small Business Costs and Transfers as a Percentage of Receipts

Receipts Size ($1,000)	Labs	Average Receipts	Total Costs per Lab	Costs as a % of Receipts	Total Transfers per Lab	Transfers as a % of Receipts
< $150	166	$75,755	$4,395	5.8%	$76	0.10%
$151 - $999	327	$430,532	$24,978	5.8%	$434	0.10%
$1000 - $1,999	145	$1,172,533	$68,026	5.8%	$1,181	0.10%
$2,000 - $3,999	169	$2,601,807	$150,947	5.8%	$2,621	0.10%
$4,000 - $5,999	120	$5,733,410	$332,631	5.8%	$5,775	0.10%
$6,000 - $9,999	51	$9,459,407	$548,799	5.8%	$9,528	0.10%
$10,000 - $14,999	27	$12,425,958	$720,908	5.8%	$12,516	0.10%
$15,000 - $19,999	40	$17,395,652	$1,009,231	5.8%	$17,521	0.10%

[94] Although businesses with gross receipts of $100 million or less are eligible to pay a reduced fee, we estimate the transfers per firm by receipts size category using the total transfers paid proportional to the share of IVDs offered as LDTs per receipt category in Table B.3 column D in Appendix B. For example, for firms making less than $150,000 in annual revenues, their share of total annual fees would be equivalent to 0.12% or $95 divided by $81,816 of the low estimate of total annualized fees of $2331 million.

$20,000 - $24,999	28	$23,750,766	$1,377,930	5.8%	$23,922	0.10%
$25,000 - $29,999	7	$29,082,108	$1,687,235	5.8%	$29,292	0.10%
$30,000 - $39,999	15	$33,924,383	$1,968,166	5.8%	$34,169	0.10%
$40,000 - $49,999	5	$49,317,674	$2,861,227	5.8%	$92,157	0.19%
$50,000 - $99,999	24	$52,498,495	$3,045,766	5.8%	$106,083	0.20%
$100,000 +	68	$209,184,656	$12,136,110	5.8%	$422,695	0.20%
Total	1,193	$16,841,846	$977,101	5.8%	$30,296	0.18%
<$41.5 M	1,097	$4,009,525	$232,618	5.8%	$4,069	0.10%
Percent small	92%	24%	24%	100%	13%	56.42%

C. Alternatives to Minimize the Burden on Small Entities

Regulatory alternative 3, described in section II.J, would reduce costs for all laboratories by extending the phaseout period to ten years for small entities and six years for other entities. Below we show how the reduction in cost under the alternative would reduce the cost on small laboratories, if it were implemented.

The alternative that could reduce the impact to small entities would be an extended phaseout policy from 4 years to 10 years for small laboratories as discussed in section II.J.3 ("third alternative"). Compared with the final phaseout policy, small laboratories would have lower one-time and recurring costs for Stage 2 of the third alternative because they generally would have an additional one to two years before FDA would expect compliance with these requirements (e.g., labeling, registration and listing, investigational use, and QS requirements). There would also be an additional 3.5 years for the compliance expectations for PMA requirements and 6 years for the compliance expectations for 510(k) and De Novo requirements. The costs associated with Stage 1 would be unimpacted by the extended phaseout policy as the costs would still occur in the first year after issuance of the final phaseout policy.

We estimate this option would reduce total costs by $690 to $478,302 per small entity.[95] For all laboratories, total recurring costs are estimated to be 4,9 percent of their average receipts. This alternative would also reduce transfers for all laboratories offering IVDs as LDTs from an average of $4,069 to $2,055 per entity for laboratories with their annual receipts below $41.5 million, which is $2,014 less than the estimated transfers of the phaseout policy. For the smallest laboratories (with annual receipts lower than $150,000), total transfers would be 0.05% percent of receipts. See Table 49.

Table 49. Small Business Costs and Transfers as a Percentage of Receipts under Regulatory Alternative 3

Receipts Size ($1,000)	Labs	Average Receipts	Costs Per Lab (7%)	Costs as a % of Receipts	Transfers Per Lab (7%)	Transfers as a % of Receipts
< $150	166	$75,755	$3,705	4.9%	$38	0.05%
$151 - $999	327	$430,532	$21,055	4.9%	$217	0.05%
$1000 - $1,999	145	$1,172,533	$57,343	4.9%	$591	0.05%
$2,000 - $3,999	169	$2,601,807	$127,243	4.9%	$1,312	0.05%
$4,000 - $5,999	120	$5,733,410	$280,395	4.9%	$2,890	0.05%
$6,000 - $9,999	51	$9,459,407	$462,617	4.9%	$4,769	0.05%
$10,000 - $14,999	27	$12,425,958	$607,697	4.9%	$6,264	0.05%
$15,000 - $19,999	40	$17,395,652	$850,743	4.9%	$8,769	0.05%
$20,000 - $24,999	28	$23,750,766	$1,161,542	4.9%	$11,973	0.05%
$25,000 - $29,999	7	$29,082,108	$1,422,274	4.9%	$14,660	0.05%
$30,000 - $39,999	15	$33,924,383	$1,659,088	4.9%	$17,101	0.05%
$40,000 - $49,999	5	$49,317,674	$2,411,904	4.9%	$71,741	0.15%
$50,000 - $99,999	24	$52,498,495	$2,567,464	4.9%	$85,176	0.16%
$100,000 +	68	$209,184,656	$10,230,275	4.9%	$339,391	0.16%
Total	1,193	$16,841,846	$823,658	68.5%	$23,202	0.14%
<$41.5 M	1,097	$4,009,525	$196,088	4.9%	$2,055	0.05%

[95] The difference in average costs per small lab between the final phaseout policy and the alternative 3 is from subtracting costs per lab column Table 49 from costs per lab column in Table 47. For example, taking $5,104 from Table 48 minus $4,305 in Table 49 equals $799.

IV. **References**

[1] "Preliminary Regulatory Impact Analysis; Initial Regulatory Flexibility Analysis; Unfunded Mandates Reform Act Analysis," 2023. [Online]. Available: https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.

[2] J. Rychert, R. Schmidt and J. Genzen, "Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System," *American journal of clinical pathology,* vol. 160, no. 3, p. 297–302, 2023.

[3] J. Hooftman, A. Dijkstra, I. Suurmeijer, A. van der Bij, E. Paap and L. Zwaan, "Common contributing factors of diagnostic error: A retrospective analysis of 109 serious adverse event reports from Dutch hospitals," *BMJ Quality & Safety,* 2023.

[4] L. Zwaan, M. de Brujine, C. Wagner, A. Thijs, M. Smits, G. van der Wal and D. Timmermans, "Patient record review of the incidence, consequences, and causes of diagnostic adverse events," *Archives of internal medicine,* vol. 170, no. 12, pp. 1015-1021, 2010.

[5] C. van Moll, T. Egberts, C. Wagner, L. Zwaan and M. Berg, "The Nature, Causes, and Clinical Impact of Errors in the Clinical Laboratory Testing Process Leading to Diagnostic Error: A Voluntary Incident Report Analysis," *Journal of Patient Safety,* vol. 19, no. 8, pp. 573-579, 2023.

[6] A. K. Stroobants, H. M. J. Goldschmidt and M. Plebani, "Error budget calculations in laboratory medicine: linking the concepts of biological variation and allowable medical errors," *Clinica chimica acta,* vol. 333, no. 2, pp. 169-176, 2003.

[7] G. D. Schiff and L. L. Leape, "Commentary: how can we make diagnosis safer?," *Academic Medicine,* vol. 87, no. 2, pp. 135-138, 2012.

[8] G. D. Schiff, S. Kim, R. Abrams, K. Cosby, B. Lambert, A. Elstein, S. Hasler, N. Krosnjar, R. Odwazny, M. Wisniewski and R. McNutt, "Diagnosing diagnosis errors: lessons from a multi-institutional collaborative project," *Advances in patient safety: from research to implementation,* vol. 2: concepts and methodology, 2005.

[9] ECRI, "Deep Dive: Laboratory Testing," [Online]. Available: https://web.archive.org/web/20140714191534/https:/www.ecri.org/Press/Pages/ECRI-Institute-PSO-Study-on-Lab-Test-related-Safety-Events-Finds-Most-Occurred-Outside-the-Laboratory.aspx.

[10] M. L. Graber, N. Franklin and R. Gordon, "Diagnostic error in internal medicine," *Archives of internal medicine,* vol. 165, no. 13, pp. 1493-1499, 2005.

[11] H. Singh, A. Meyer and E. Thomas, "The frequency of diagnostic errors in outpatient care: estimations from three large observational studies involving US adult populations," *BMJ Quality and Safety,* vol. 23, no. 9, pp. 727-731, 2014.

[12] New York State Department of Health, "Public Comment: Re: Food and Drug Administration Docket No. FDA-2023-N-2177 (88 FR 68006)," 22 November 2023. [Online]. Available: https://www.regulations.gov/comment/FDA-2023-N-2177-4963. [Accessed 22 December 2023].

[13] J. C. Hopewell, S. Parish, R. Clarke, J. Armitage, L. Bowman, J. Hager, M. Lathrop and R. Collins, "No Impact of KIF6 Genotype on Vascular Risk and Statin Response Among 18,348 Randomized Patients in the Heart Protection Study," *Journal of the American College of Cardiology,* vol. 57, no. 20, pp. 2000-2007, 2011.

[14] T. Assimes , H. Hólm , S. Kathiresan, M. P. Reilly, G. Thorleifsson, B. F. Voight, J. Erdmann, C. Willenborg, D. Vaidya, C. Xie, C. C. Patterson, T. M. Morgan, M. S. Burnett, M. Li, M. A. Hlatky, J. W. Knowles, J. R. Thompson, D. Absher, C. Iribarren, A. Go, S. P. Fortmann, S. Sidney and N. T. Risch, "Lack of Association Between the Trp719Arg Polymorphism in Kinesin-Like Protein-6 and Coronary Artery Disease in 19 Case-Control Studies," *J American College of Cardiology,* pp. 1552-1563, 2010.

[15] S. Kliff and A. Bhatia, "When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong," *New York Times,* 1 January 2022.

[16] Centers for Disease Control and Prevention, "Division of Laboratory Systems (DLS): Strengthening Clinical Laboratories," 15 November 2018. [Online]. Available: https://www.cdc.gov/csels/dls/strengthening-clinical-labs.html. [Accessed 21 August 2023].

[17] Grand View Research, "Laboratory Developed Tests Market Size, Share & Trends Analysis Report By Technology (Immunoassay, Molecular Diagnostics), By Application (Oncology, Nutritional & Metabolic Disease), By Region, And Segment Forecasts, 2023 - 2030," Grand View Research, San Francisco, 2023.

[18] Centers for Medicare & Medicaid Services, "Clinical Laboratory Improvement Amendments (CLIA) Post-Public Health Emergency (PHE) Guidance," 11 May 2023. [Online]. Available: https://www.cms.gov/files/document/qso-23-15-clia.pdf. [Accessed 21 August 2023].

[19] Centers for Medicare and Medicaid Services, "CLIA Overview," 22 October 2013. [Online]. Available: https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ldt-and-clia_faqs.pdf. [Accessed 18 January 2024].

[20] U.S. Food and Drug Administration, "Memorandum to File from Brittany Schuck Re: Examples of In Vitro Diagnostic Products (IVDs) Offered as Laboratory Developed Tests

(LDTs) that Raise Public Health Concerns," 2023. [Online]. Available: https://www.regulations.gov/document/FDA-2023-N-2177-0076.

[21] J. D. Pfeifer, R. Loberg, C. Lofton-Day and B. A. Zehnbauer, "Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics," *American Journal of Clinical Pathology,* pp. 157(4):628-638, 2022.

[22] U.S. Food and Drug Administration, "Letter to deCODEme Complete Scan," 2010. [Online]. Available: https://www.fda.gov/media/79216/download.

[23] U.S. Food and Drug Administration, "Letter to 23andMe Personal Genome Service," 2010. [Online]. Available: http://web.archive.org/web/20191214010336/https:/www.fda.gov/media/79205/download.

[24] American Association for Cancer Research, "Re: Request for Information Regarding 21st Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests," 5 January 2015. [Online]. Available: https://www.aacr.org/wp-content/uploads/2019/11/AACR-Comments-Modernized-Framework-Diagnostics-Jan-5-2015.pdf. [Accessed 24 August 2023].

[25] U.S. Government Publishing Office, "Laboratory Testing in the Era of Precision Medicine," 20 September 2016. [Online]. Available: https://www.govinfo.gov/content/pkg/CHRG-114shrg21906/pdf/CHRG-114shrg21906.pdf. [Accessed 24 August 2023].

[26] U.S. Food and Drug Administration, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs); Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories," 3 October 2014. [Online]. Available: https://www.fda.gov/media/89841/download. [Accessed 23 August 2023].

[27] Pew Research Center, "The Role of Lab-Developed Tests in the In Vitro Diagnostics Market.," 22 10 2021. [Online]. Available: https://www.pewtrusts.org/en/research-and-analysis/reports/2021/10/the-role-of-lab-developed-tests-in-the-in-vitro-diagnostics-market.

[28] U.S. Food and Drug Administration, "Memo to File: Information from the New York State Department of Health (NYSDOH) for the Preliminary Regulatory Impact Analysis for the Laboratory Developed Tests Proposed Rule and Certain Related Analysis," 2023.

[29] Department of Health, Wadsworth Center, "Clinical Laboratory Evalualation Program: Clinical Laboratories: Obtain a Permit: Test Approval," [Online]. Available: https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval. [Accessed 21 August 2023].

[30] Congressional Budget Office, "Federal Policies in Response to Declining Entrepreneurship," 29 December 2020. [Online]. Available: https://www.cbo.gov/publication/56945. [Accessed 21 August 2023].

[31] AstuteAnalytica India Pvt. Ltd., "United States Clinical Laboratory Services Market to Generate Revenue of US$ 125.6 Billion by 2030: Astute Analytica," 13 March 2023. [Online]. Available: https://www.globenewswire.com/news-release/2023/03/13/2625730/0/en/United-States-Clinical-Laboratory-Services-Market-to-Generate-Revenue-of-US-125-6-Billion-by-2030-Astute-Analytica.html. [Accessed 21 August 2023].

[32] U.S. Food and Drug Administration, "Performance Report to Congress: Medical Device User Fee Amendments, FY 2022, page 21," 2022. [Online]. Available: www.fda.gov/media/167825/download. [Accessed 21 August 2023].

[33] D. E. Newman-Toker, Z. Wang, Y. Zhu, N. Nassery, A. S. Saber Tehrani, A. C. Schaffer, C. W. Yu-Moe, G. D. Clemens, M. Fanai and D. Siegal, "Rate of diagnostic errors and serious misdiagnosis-related harms for major vascular events, infections, and cancers: toward a national incidence estimate using the “Big Three”," *Diagnosis,* vol. 8, no. 1, pp. 67-84, 2021.

[34] D. Newman-Toker, N. Nassery, A. Schaffer, C. W. Yu-Moe, G. D. Clemens, Z. Wang, Y. Zhu, A. S. S. Tehrani, M. Fanai, A. Hassoon and D. Siegal, "Burden of serious harms from diagnostic error in the USA," *BMJ Quality & Safety,* 2023.

[35] D. Newman-Toker, A. Schaffer, W. Yu-Moe, N. Nassery, A. S. Tehrani, G. Clemens, Z. Wang, Y. Zhu, M. Fanai and D. Siegal, "Serious misdiagnosis-related harms in malpractice claims: The "Big Three" - vascular events, infections, and cancers," *Diagnosis,* vol. 6, no. 3, pp. 227-240, 2019.

[36] U.-P. Rohr, C. Binder, T. Dieterle, F. Giusti, C. G. M. Messina, E. Toerien, H. Moch and H. H. Schafer, "The Value of In Vitro Diagnostic Testing in Medical Practice: A Status Report," *PLOS One,* vol. 11, no. 3, pp. 1-16, 2016.

[37] M. M. Ward, F. Ullrich, K. Matthews, G. Rushton, M. A. Goldstein, D. F. Bajorin, A. Hanley and C. F. Lynch, "Who Does Not Receive Treatment for Cancer?," *Journal of Oncology Practice,* vol. 9, no. 1, pp. 20-6, 2013.

[38] National Cancer Institute, "Cancer Stat Facts: Common Cancer Sites," 2023. [Online]. Available: https://seer.cancer.gov/statfacts/html/common.html. [Accessed 21 August 2023].

[39] National Cancer Institute, "Age and Cancer Risk," National Institutes of Health, 5 March 2021. [Online]. Available: https://www.cancer.gov/about-cancer/causes-prevention/risk/age. [Accessed 18 August 2023].

[40] P. A. Johnstone, M. S. Norton and R. H. Riffenburgh, "Survival of patients with untreated breast cancer," *Journal of Surgical Oncology,* vol. 73, no. 4, pp. 273-277, 2000.

[41] H. Wao, R. Mhaskar, A. Kumar, B. Miladinovic and B. Djulbegovic, "Survival of patients with non-small cell lung cancer without treatment: a systematic review and meta-analysis," *Systematic Reviews,* vol. 2, no. 10, 2013.

[42] U.S. Department of Health and Human Services, "Guidelines for Regulatory Impact Analysis," 12 Jan 2017. [Online]. Available: https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis.

[43] American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee, "Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association," American Heart Association, 2023.

[44] Centers for Disease Control and Prevention, "Heart Disease Facts," 15 May 2023. [Online]. Available: https://www.cdc.gov/heartdisease/facts.htm#print. [Accessed 27 November 2023].

[45] Z. Raisi-Estabragh, O. Kobo, A. Elbadawi, P. Velagapudi, G. Sharma, R. Bullock-Palmer, S. Petersen, L. Mehta, W. Ullah, A. Roguin, L. Sun and M. Mamas, "Differential Patterns and Outcomes of 20.6 Million Cardiovascular Emergency Department Encounters for Men and Women in the United States," *Journal of the American Heart Association,* vol. 11, no. 19, p. e026432, 2022.

[46] J. Conly, F. Clement, M. Tonelli, B. Hemmlgarn, S. Klarenbach, A. Lloyd and F. McAlister, "Cost-effectiveness of the use of low- and high-potency statins in people at low cardiovascular risk.," *CMAJ,* 2011.

[47] U.S. Department of Health and Human Services, "Contractor Project Report: International Prescription Drug Price Comparisons: Estimates Using 2022 Data," U.S. Department of Health and Human Services, 2024.

[48] Centers for Disease Control and Prevention, "National Notifiable Diseases Surveillance System. 2019 annual tables of infectious disease data," 2021. [Online]. Available: https://www.cdc.gov/nchs/hus/contents2020-2021.htm#Table-IDNotif. [Accessed 31 January 2024].

[49] Y. Li, S. You, K. Lee, R. Yaesoubi, K. Hsu, T. Gift, H. Chesson, A. Berruti, J. Salomon and M. Ronn, "The Estimated Lifetime Quality-Adjusted Life-Years Lost Due to Chlamydia, Gonorrhea, and Trichomoniasis in the United States in 2018," *The Journal of Infectious Diseases,* vol. 227, no. 8, pp. 1007-1018, 2023.

[50] A. Malek, C.-C. Chang, D. Clark and R. Cook, "Delay in Seeking Care for Sexually Transmitted Diseases in Young Men and Women Attending a Public STD Clinic," *Open AIDS Journal,* vol. 14, no. 7, pp. 7-13, 2013.

[51] Blue Cross and Blue Shield of Minnesota, "Blue Cross and Blue Shield of Minnesota Files Lawsuit Against GS Labs," 1 March 2022. [Online]. Available:

https://www.bluecrossmn.com/about-us/newsroom/news-releases/blue-cross-and-blue-shield-minnesota-files-lawsuit-against-gs-labs. [Accessed 21 August 2023].

[52] APM Reports, "GS Labs' responses to questions from APM Reports," APM Reports, 28 7 2022. [Online]. Available: https://www.apmreports.org/story/2022/07/28/gs-labs-responses-to-questions-from-apm-reports. [Accessed 10 1 2024].

[53] T. Scheck, J. Lu, W. Callan and A. Canny, "Private COVID lab created headaches for Minnesota consumers, health officials," 28 July 2022. [Online]. Available: https://www.mprnews.org/story/2022/07/28/gs-labs-covid-testing-minnesota. [Accessed 21 August 2023].

[54] D. McKnight and P. Hinton, "Tort Costs in America: An Empirical Analysis of Costs and Compensation of the U.S. Tort System," 22 November 2022. [Online]. Available: https://instituteforlegalreform.com/research/tort-costs-in-america-an-empirical-analysis-of-costs-and-compensation-of-the-u-s-tort-system/. [Accessed 21 August 2023].

[55] U.S. Food and Drug Administration, "Summary; Medical Device Reporting: Electronic Submission Requirements Final Regulatory Impact Analysis," 14 Feb 2014. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/summary-medical-device-reporting-electronic-submission-requirements-final-rule.

[56] U.S. Food and Drug Administration, "Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals," 11 Aug 2023. [Online]. Available: https://www.regulations.gov/document/FDA-2023-N-1006-0002.

[57] U.S. Food and Drug Administration, "Medical Devices; Quality System Regulation Amendments (Proposed Rule) Preliminary Regulatory Impact Analysis," 02 03 2022. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/medical-devices-quality-system-regulation-amendments-proposed-rule-preliminary-regulatory-impact. [Accessed 25 01 2024].

[58] U.S. Food and Drug Administration, "Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs that Are Regulated Under a Biologics License Application, and Animal Drugs," Aug 2016. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/requirements-foreign-and-domestic-establishment-registration-and-listing-human-drugs-including-drugs.

[59] U.S. Food and Drug Administration, "Summary: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling Final Regulatory Impact Analysis," Dec 2014. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/summary-

content-and-format-labeling-human-prescription-drug-and-biological-products-requirements.

[60] J. V. Batavia and S. J. Goldenberg, "Strategic Planning and Costs of FDA Regulation," *Academic Entrepreneurship for Medical and Health Scientists,* vol. 1, no. 2, 2019.

[61] I. Eastern Research Group, "Economic Analysis of CDRH Submission Requirements," 2012.

[62] U.S. Food and Drug Administration, "Microbiology Devices; Reclassification of Nucleic Acid-Based Systems for Mycobacterium tuberculosis complex Final Regulatory Impact Analysis," 2014. [Online]. Available: https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/summary-microbiology-devices-reclassification-nucleic-acid-based-systems-mycobacterium-tuberculosis.

[63] U.S. Food and Drug Administration, "Food Safety Modernization Act Domestic and Foreign Facility Reinspection, Recall, and Importer Reinspection Fee Rates for Fiscal Year 2024," 28 July 2023. [Online]. Available: https://www.federalregister.gov/documents/2023/07/28/2023-15927/food-safety-modernization-act-domestic-and-foreign-facility-reinspection-recall-and-importer. [Accessed 20 October 2023].

[64] U.S. Food and Drug Administration, "Discussion Paper on Laboratory Developed Tests (LDTs)," 13 January 2017. [Online]. Available: https://www.fda.gov/media/102367/download. [Accessed 30 March 2023].

[65] G. S. Gerhard, S. G. Fisher and A. M. Feldman, "Genetic Testing for Inherited Cardiac Diseases in Underserved Populations of Non-European Ancestry: Double Disparity," *JAMA Cardiology,* pp. 3(4):273-274, 2018.

[66] A. K. Manrai, B. H. Funke, H. L. Rehm, M. S. Olesen, B. A. Maron, P. Szolovits, D. M. Margulies, J. Loscalzo and I. S. Kohane, "Genetic Misdiagnoses and the Potential for Health Disparities," *New England Journal of of Medicine,* pp. 375:655-665, 2016.

[67] A. R. Martin, M. Kanai, Y. Kamatani, Y. Okada, B. M. Neale and M. J. Daly, "Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities," *Nature Genetics,* pp. 51,584-591, 2019.

[68] Y. Wang, K. Tsuo, M. Kanai, B. M. Neale and A. R. Martin, "Challenges and Opportunities for Developing More Generalizable Polygenic Risk Scores," *Annual Review of Biomedical Data Science,* pp. 5:293-320, 2022.

[69] L. Duncan, H. Shen, B. Gelaye, J. Meijsen, K. Ressler, M. Felman, R. Peterson and B. Domingue, "Analysis of Polygenic Risk Score Usage and Performance in Diverse Human Populations," *Nature Communications,* p. 10(1):3328, 2019.

[70] K. F. Hoskins, O. C. Danciu, N. Y. Ko and G. S. Calip, "Association of Race/Ethnicity and the 21-Gene Recurrence Score With Breast Cancer–Specific Mortality Among US Women," *JAMA Oncology,* pp. 7(3):370-378, 2021.

[71] J. Gruber, " Chapter2," in *PublicFinanceandPublicPolicy,*, WorthPublishers,, 2016.

[72] Federal Reserve Bank of San Francisco, "Federal Reserve Bank of San Francisco Education Publications," November 2002. [Online]. Available: https://www.frbsf.org/education/publications/doctor-econ/2002/november/private-social-costs-pollution-production/#fn. [Accessed 21 August 2023].

[73] Congressional Research Service, "FDA Regulation of Laboratory-Developed Tests (LDTs)," 7 December 2022. [Online]. Available: https://crsreports.congress.gov/product/pdf/IF/IF11389. [Accessed 23 August 2023].

[74] J. K. Hammitt and J.-T. Liu, "Effects of Disease Type and Latency on the Value of Mortality Risk," *Journal of Risk and Uncertainty,* vol. 28, pp. 73-95, 2004.

[75] J. Hickner, P. Thompson, T. Wilkinson, P. Epner, M. Shaheen, A. Pollock, J. Lee, C. Duke, B. Jackson and J. Taylor, "Primary Care Physicians' Challenges in Ordering Clinical Laboratory Tests and Interpreting Results," *The Journal of the American Board of Family Medicine,* vol. 27, no. 2, pp. 268-274, 2014.

Appendix A. Estimation of the Number of Affected Labs and Tests

Number of Affected Labs

To obtain the number of laboratories and tests affected by the phaseout policy, we use data from the Centers for Medicare & Medicaid Services (CMS) that shows the number of laboratories by laboratory type (column A in Table A.1).[96] Only laboratories that are certified under CLIA and meet the regulatory requirements under CLIA to perform high complexity testing are affected by the phaseout policy since LDTs are high complexity. To determine the number of affected high complexity laboratories, we must first determine the number of non-waived laboratories (column C in Table A.1) and then estimate how many of those can perform high complexity testing versus only moderate complexity testing. We determine the number of non-waived laboratories by excluding the number of laboratories whose certificate type is microscopy or waiver (column B in Table A.1). Since laboratories are certified only as waived or non-waived, without specific notation on whether they meet the regulatory requirements for high complexity testing or only moderate complexity testing, the estimate for how many of the non-waived laboratories can perform high complexity testing is based on FDA professional judgement and historical knowledge. Therefore, we estimated the percent of each laboratory type that was likely to be high complexity to determine the high complexity rate (column D). We then estimate the number of high complexity laboratories affected by the phaseout policy by multiplying column C times high complexity rate in column D (column E). We estimate that there are 11,808 high complexity CLIA laboratories. This is close to our original estimate of 12,000 used in the preliminary analysis (Ref. [1]) and a 2021 report from the Pew Charitable

[96] https://qcor.cms.gov/advanced_find_provider.jsp?which=4&backReport=active_CLIA.jsp

Trust (Ref. [12]) that also estimated that there are approximately 12,000 CLIA-certified laboratories performing high complexity testing.

As explained in section II.D.1, we rely on the information about laboratories and tests in NYS to estimate the percent of high complexity laboratories that make IVDs offered as LDTs. From the NYSDOH data, we calculate that approximately 10% of laboratories located in NYS that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing are developing IVDs offered as LDTs. We assume that NYS is representative of the U.S. laboratory community. We therefore estimate that approximately 10% of 11,808 (or 1,181) laboratories in the U.S. that are certified under CLIA and that meet the regulatory requirements under CLIA to perform high complexity testing currently manufacture IVDs offered as LDTs. To account for potential variability across the country, we estimate the proportion of high complexity laboratories making IVDs offered as LDTs to vary from 5% of 11,808 (or 590) laboratories to a high estimate of 20% of 11,808 (or 2,362) affected laboratories by reducing the primary estimate by 50% and doubling the primary estimate, respectively. In addition, we assume that there would be new laboratories entering the market every year (approximately 8 percent of the affected high complexity laboratories making IVDs offered as LDTs, ranging from 47 to 189, with a primary estimate of 94). While there are also likely laboratories that exit the market each year, we have not subtracted expected departing laboratory numbers from our cost estimates.

Table A.1 Number of Affected Laboratories by Laboratory Type

Laboratory Type	(A) Total	(B) Waiver and Microscopy	(C) Difference (A) - (B)	(D) High Complexity Rate	(E) No. HC Labs (C) x (D)	(F) Integrated Healthcare System Rate	(G) No. HC Labs within Healthcare System (E) x (F)
Physician Office **	123,726	108,696	15,030	0	-		-
Other **	39,524	36,162	3,362	0.5	1,681	0	-

Pharmacy**	29,120	29,110	10	0	-		-
Intermediate Care Facility *	28,758	28,705	53	0	-		-
Skilled Nursing/ Nursing Facility	15,154	15,109	45	0	-		-
Home Health Agency	13,824	13,809	15	0	-		-
Assisted Living Facility	12,019	12,015	4	0	-		-
Hospital	9,399	2,599	6,800	0.5	3,400	1	3,400
Independent	9,198	3,602	5,596	0.75	4,197	0	-
Community Clinic	8,165	6,686	1,479	0.5	740	0.66	488
End Stage Renal Disease Dialysis	7,301	7,294	7	0	-		-
Ambulatory Surgery Center	7,150	6,719	431	0.75	323	0.5	162
Other Practitioner	6,868	6,653	215	0	-		-
School/Student Health Service	6,729	6,599	130	0	-		-
Ambulance	5,968	5,917	51	0	-		-
Hospice	5,100	5,091	9	0	-		-
Federally Qualified Health Center	4,556	4,332	224	0.5	112	0	-
Ancillary Test Site	3,700	2,811	889	0.75	667	0.5	333
Mobile Lab	3,219	3,131	88	0.25	22	0.75	17
Rural Health Care Clinic	2,726	2,512	214	0.25	54	0.25	13
Industrial	1,771	1,751	20	0.5	10	0	-
Comprehensive Outpatient Rehab	1,230	1,214	16	0.5	8	0.5	4
Prison	1,204	1,168	36	0.5	18	0	-
Public Health Laboratory	1,015	777	238	1	238	0	-
Health Maintenance Org	695	536	159	0.5	80	0.5	40
Health Fair	617	608	9	0	-		-
Blood Banks	426	167	259	1	259	0.5	130
Insurance	45	42	3	0	-		-
Total	**349,207**	**313,815**	**35,392**		**11,808**		**4,586**

Number of Affected Tests

We estimate the number of affected tests using information from NYSDOH. We then estimate the number of affected tests subject to different requirements and that would fall under different enforcement policies by adjusting the number of tests to account for the number that are

currently marketed, the number expected to be impacted by potential reclassification of Class III IVDs to Class II IVDs, the number of LDTs expected to be for unmet needs in an integrated health care system, and the number of LDTs estimated to be reviewed by NYS CLEP each year.

1) Using NYSDOH information

Using the NYSDOH information, FDA calculates that each laboratory that manufactures IVDs offers an average of 67 IVDs as LDTs and introduces an average of 6 new IVDs offered as LDTs per year (see section II.D.1 for details of the calculation). Multiplying 67 IVDs per lab by the number of affected laboratories, it is estimated that the number of affected currently marketed IVDs offered as LDTs ranges from 39,557 (=590 x 67) to 158,227 (=2,362 x 67), with a primary estimate of 79,114 (=1,181 x 67). Multiplying 6 new IVDs offered as LDTs per laboratory by the number of affected laboratories, we estimate 3,542, 7,085, or 14,170 new IVDs offered as LDTs may be affected per year.[97] We also estimate new IVDs offered as LDTs from new laboratories entering the market every year (8 percent of affected laboratories). The total number of new IVDs offered as LDTs per year is estimated to range from 3,826 to 15,303, with a primary estimate of 7,652.

FDA generally intends to exercise enforcement discretion with respect to premarket review requirements for currently marketed IVDs offered as LDTs and LDTs manufactured and performed by a laboratory integrated within a healthcare system to meet an unmet need of patients receiving care within the same healthcare system. To estimate the number of high complexity laboratories within integrated healthcare systems which may fall under the enforcement discretion policy for unmet needs (column G in Table A.1 above), we first multiply

[97] As mentioned in Section D.1, we only rely on the NYSDOH information to extrapolate estimates for affected tests across the country and assume that the laboratories in NYS are representative of the U.S. laboratory community. The estimates thus may be biased upwards if the costs associated with premarket review of IVDs offered as LDTs result in fewer new IVDs per year.

the number of high complexity laboratories in each laboratory type in each row in Column E by the estimated rate of integrated healthcare system in Column F for that laboratory type. As with the high complexity rate, to determine the estimated rate of integrated healthcare system laboratories, we used professional judgement and historical knowledge to estimate the percent of high complexity laboratories we expect would be part of an integrated healthcare system for each laboratory type. We estimate that there are approximately 4,586 high complexity laboratories that may be part of an integrated healthcare system. Applying the proportion of high complexity laboratories making IVDs offered as LDTs (5%, 10%, 20%) to this estimate, we estimate the number of high complexity laboratories with LDTs within integrated healthcare systems to range from 229 (=5% x 4,586) to 917 (=20% x 4,586), with a primary estimate of 459 (=10% x 4,586). We assume that about 40 to 70 percent of LDTs from these high complexity laboratories integrated within healthcare systems are likely to be for unmet needs. The estimated number of LDTs that are likely to be for unmet needs range from 10,755 to 24,582, with a primary estimate of 16,900 (see Table A.2).

Table A.2 Number of Affected Laboratories and LDTs For Unmet Needs

Number of affected labs and tests	Primary	Low	High	Calculation
Affected labs **(A)**	1,181	590	2,362	11,808 * 5-20%
Affected IVDs offered as LDTs on the market **(B)**	79,114	39,557	158,227	A * 67
New IVDs offered as LDTs per year **(C)**	7,652	3,826	15,303	A * 1.08 * 6
Affected labs for unmet needs **(D)**	459	229	917	4,586 * 5-20%
Affected LDTs on the market for unmet needs **(E)**	16,900	10,755	24,582	D * 67 * 40-70%
New LDTs for unmet needs **(F)**	1,635	1,040	2,377	D * 1.08 * 6 * 40-70%
Affected IVDs offered as LDTs on the market excluding LDTs for unmet needs	62,213	28,802	133,645	B - E
New IVDs offered as LDTs excluding LDTs for unmet needs	6,017	2,786	12,926	C - F

Note: *Product across table may not be exact due to rounding.*

Table A.3 shows the number of affected IVDs offered as LDTs by submission type, excluding tests for unmet needs, using the primary estimates from Table A.2. As explained in section II.D.1, we also expect that among currently-marketed IVDs offered as LDTs that were first marketed prior to the date of issuance of the rule, 2 IVDs will be modified per laboratory per year in a manner that falls outside of the enforcement discretion policy for currently marketed IVDs offered as LDTs and will thus be expected to undergo premarket review (2,362 = 1,181 affected labs * 2). We then add this number to the number of new tests (10,013 = 2,362 + 7,652) to estimate total number of new tests in column A of Table A.3. We further break down these estimates by submission type to estimate compliance costs. As mentioned in section II.F.2, we estimate that approximately 50 percent of IVDs currently undergo premarket review (5,007 = 10,013 * 0.5). In addition, we assume that about 40 percent are offered after 510(k) clearance (4,005 = 10,013 * 0.40), 5 percent after De Novo classification (501 = 10,013 * 0.05), and 5 percent after premarket approval (501 = 10,013 * 0.05). We assume these estimated percentages also apply to IVDs offered as LDTs and apply these shares to the estimated total number of affected tests, minus the number of affected tests expected to be offered under an enforcement policy without premarket submission, to estimate the number of IVDs offered as LDTs by submission type. For 2,139 LDTs for unmet needs (2,139 = 459 * 2 * 55% + 1,635)[98], we estimate that approximately 10 percent are offered after premarket approval (214 = 2,139 * 0.10), 80 percent after 510(k) clearance (1,711 = 2,139 * 0.80), and 10 percent after De Novo classification (214 = 2,139 * 0.10). We then subtract the number of new LDTs for unmet needs (column B of Table A.3) from the number of new IVDs offered as LDTs (column A of Table A.3) to calculate the number of new IVDs offered as LDTs excluding LDTs for unmet needs.

[98] We assume that about 40 to 70 percent of LDTs from these high complexity laboratories integrated within a healthcare system are likely to be for unmet needs. We use 55% for the primary estimate.

Table A.3 Number of IVDs offered as LDTs Per Year Excluding LDTs For Unmet Needs

	No. IVDs offered as LDTs, total A	No. LDTs for unmet needs B	No. IVDs offered as LDTs excluding LDTs for unmet needs A - B
Total	10,013	2,139	7,874
Exempt	5,007	-	5,007
PMA	501	214	287
510 (k)	4,005	1,711	2,294
De Novo	501	214	287

2) Reclassification adjustment

On January 31, 2024, FDA announced its intent to initiate the reclassification process for most IVDs that are currently Class III into Class II. The majority of these tests are infectious disease and companion diagnostic IVDs. Reclassification would allow manufacturers of certain types of tests to seek marketing clearance through the less burdensome 510(k) pathway rather than the PMA pathway. FDA also intends to continue taking a risk-based approach in the initial classification of IVDs to determine the appropriate level of regulatory controls and whether a new test may be classified into Class II through De Novo classification (and special controls established), rather than being class III and subject to the PMA pathway. Based on our experience, we believe that special controls could be developed that, along with general controls, could provide a reasonable assurance of safety and effectiveness for most future companion diagnostic and infectious disease IVDs. As such, first of a kind submission for such tests would be expected to submit a De Novo, with follow-on IVDs submitting 510(k) notifications. Therefore, our estimates for the number of affected IVDs that will be subject to certain requirements were adjusted based on the anticipated number of submissions following the potential reclassifications and considering that most future companion diagnostic and infectious disease IVDs would be reviewed through the De Novo and 510(k) pathways.

To estimate anticipated rates of submissions going forward, we rely on historical data for total IVD original and supplemental PMA submissions where FDA review started in the last ten fiscal years (FY 2014-2023). We use information for IVD PMA submissions received per fiscal year for certain CDRH-regulated infectious disease and companion diagnostic tests that have either been recently down classified or for which FDA intends to propose reclassification (Table A.4). The number of estimated De Novo submissions per year going forward is estimated based on the number of "first of a kind (FOAK)" original PMA submissions since, going forward, we would expect new FOAK tests to submit a De Novo instead of a PMA. The number of estimated 510(k) submissions per year going forward is estimated by considering the number of non-FOAK original PMA submissions as well as PMA supplements since, going forward, we would expect these submissions to be 510(k)s instead. (We excluded "135-Day Review Track for 30-Day Notice" and "Special CBE" PMA supplement types from our counts since no 510(k) would be expected for these types of modifications for Class II devices).

We use these data to calculate the reduction in anticipated PMA submissions and the increase in anticipated De Novo and 510(k) submissions going forward, following potential reclassification and considering that most future companion diagnostic and infectious disease IVDs would be Class II. This is represented by the last three columns of Table A.4, showing the rate of remaining PMAs, the rate of new De Novos, and the rate of new 510(k)s anticipated per year, respectively. Then we use these rates to determine the new estimates, as shown in Table A.5. For example, we multiply the remaining PMA rate (Column F of Table A.4) of 0.40 by the estimated number of PMAs before potential reclassification (Table A.5) to obtain the number of PMAs expected after potential reclassification (287 * 0.40 = 115) (Table A.5). We then multiply the De Novo rate of 0.06 (Column G of Table A.4) by the number of PMAs before potential

reclassification and add to the number of De Novo submissions before potential reclassification to estimate the number of De Novo submissions after potential reclassification (287 * 0.06 + 287 = 304) (Table A.5).

Table A.4 Rate of Potential Reclassification of PMA Submission Per Fiscal Year (FY 2014-2023)

Review Track	**(A)** Average Historical IVD submissions per Year	**(B)** # from column A that fall into procodes considered for reclassification	**(C)** Average FOAK used to estimate future # De Novo per Year	**(D)** Average non-FOAK used to estimate future # 510(k) per Year	**(E)** Estimated # Remaining PMA per year in future	**(F) Remaining PMA Rate =(E)/(A)**	**(G) De Novo Rate =(C)/(A)**	**(H) 510(k) Rate =(D)/(A)**
PMA Original	11.7	7.0	0.7	6.3	4.7	0.40	0.06	0.54
135 Review Track For 30-Day Notice	13.7	5.3	0.0	0.0	8.4	0.61	0.00	0.00
Normal 180 Day Track	27.4	17.3	0.0	17.3	10.1	0.37	0.00	0.63
Normal 180 Day Track No User Fee	15.8	9.4	0.0	9.4	6.4	0.41	0.00	0.59
Panel Track	7.7	4.8	0.0	4.8	2.9	0.38	0.00	0.62
Real-Time Process	53.3	25.9	0.0	25.9	27.4	0.51	0.00	0.49
Special CBE	11.3	5.5	0.0	0.0	5.8	0.51	0.00	0.00

Table A.5 Number of Submissions for IVDs offered as LDTs Before and After Potential Reclassification

Submission Type	**Before Potential Reclassification**			**After Potential Reclassification**		
	Primary	Low	High	Primary	Low	High
PMA	287	143	574	115	58	230
510(k)	2,294	1,147	4,588	2,479	1,239	4,958
De Novo	287	143	574	304	152	608
PMA supplements	67	33	133	35	17	70

3) NYS CLEP review adjustment

As discussed in the preamble, FDA intends to exercise enforcement discretion and generally not enforce premarket review requirements for LDTs that are approved by NYS CLEP. Therefore, we reduce the estimated number of premarket submissions to FDA by the number of premarket submissions expected to go to NYS CLEP. We use an estimate of the number of

premarket submissions expected to be reviewed by NYS CLEP, rather than an estimate of the number of LDTs expected to be approved by NYS CLEP, due to the assumption that neither NYS CLEP nor FDA will approve/authorize 100% of the submissions reviewed, and workload costs are based on the number of submissions reviewed, not the number approved/authorized.

NYSDOH provided information indicating that they review an average of 888 LDTs per year, including high risk, moderate risk, low risk, and clinical trial IVDs based on NYSDOH criteria. Accounting for FDA's assumption that 50% of IVDs offered as LDTs will be low risk and not subject to premarket review and that 21% of new IVDs offered as LDTs per year will fall within the enforcement discretion policy for unmet needs (0.21 = 1,635 new LDTs for unmet needs per year / 7,652 new IVDs offered as LDTs per year; see Table A.2), we estimate that an average of 351 (= [100% - 21%] x 50% x 888) new IVDs offered as LDTs per year that would normally be submitted to FDA for premarket review would not undergo FDA premarket review as a result of the enforcement discretion policy with respect to LDTs approved by NYS CLEP . We then estimate that 12.1% of premarket submissions for IVDs offered as LDTs would be reviewed by NYS CLEP (and that these would not be submitted to FDA for review) by dividing 351 by 2,898 (the total number of new PMAs, 510(k)s, and De Novo submissions per year for affected tests, see Table A.5), excluding those that would be under the unmet needs enforcement discretion policy (0.121 = 351 / 2,898).

We thus exclude 12.1% from the number of affected tests after potential reclassification (Table A.5). Table A.6 below shows the final number of premarket submissions for IVDs offered as LDTs, excluding tests for unmet needs and submissions for LDTs expected to be reviewed by NYS CLEP, when estimating the costs of Stages 4 and 5 in section II.F.4. For example, we estimate the number of PMAs to be 101 (=115 – 115*0.121).

Table A.6 Number of IVD Submissions After Potential Reclassification and Excluding Tests for Unmet Needs and LDTs Reviewed by NYS CLEP

Submission Type	Primary	Low	High
PMA	101	51	203
510(k)	2,179	1,090	4,359
De Novo	267	134	534
PMA supplements	31	15	61

Appendix B. Final Small Entity Analysis Estimates

The purpose of this Appendix is to explain the steps for calculating the number of laboratories and existing IVDs offered as LDTs per receipt size category that was used for Section III. Final Small Entity Analysis. In Table 48 of Section III. Final Small Entity Analysis, we used detailed data from 2017 Statistics of U.S. Businesses on U.S. 6-digit NAICS detailed employment sizes and revenues to analyze the potential impacts of the phaseout policy on small entities. We initially use our estimated total market revenue for IVDs offered as LDTs of $14 billion in the bottom of column E in Table B.1 as our total annual receipts and extrapolate the share of annual receipt by enterprise size from the 2017 Census data corresponding to NAICS code 621511. This estimate is based on the assumption that 35% of revenue for this NAICS category is from IVDs offered as LDTs.[99] We also re-classify enterprise size categories given our new estimated average receipts per lab (Table B.2).

Table B.1 Growth Adjusted Annual Receipts from IVDs Offered as LDTs by Enterprise Size (2022, U.S. Dollars)		
Number of Firms and Receipts by Enterprise Receipt Size 2017	**Receipts Only IVDs Offered as**	**Calculation**

[99] This is also explained in detail in section II.D.3 Baseline Market Revenue.

I	Enterprise Size ($1,000)	Firms	Receipts ($1,000) D	LDTs ($1,000) in 2022 dollars adjusted for growth since 2017 E	
1	< $150	438	$22,315	$12,575	E Total * D1/D Total
2	$151 - $999	933	$250,134	$140,954	E Total * D2/D Total
3	$1000 - $1,999	413	$301,551	$169,929	E Total * D3/D Total
4	$2,000 - $3,999	481	$779,302	$439,148	E Total * D4/D Total
5	$4,000 - $5,999	343	$1,224,596	$690,078	E Total * D5/D Total
6	$6,000 - $9,999	146	$860,008	$484,627	E Total * D6/D Total
7	$10,000 - $14,999	77	$595,808	$335,747	E Total * D7/D Total
8	$15,000 - $19,999	115	$1,245,731	$701,988	E Total * D8/D Total
9	$20,000 - $24,999	79	$1,168,397	$658,409	E Total * D9/D Total
10	$25,000 - $29,999	21	$380,304	$214,307	E Total * D10/D Total
11	$30,000 - $39,999	43	$908,377	$511,884	E Total * D11/D Total
12	$40,000 - $49,999	15	$460,659	$259,588	E Total * D12/D Total
13	$50,000 - $99,999	67	$2,190,319	$1,234,278	E Total * D13/D Total
14	$100,000 +	194	$25,270,700	$14,240,421	E Total * D14/D Total
	Total	**3,365**	$35,658,201	$20,093,935	

We estimate the number of labs by receipt size category by the same proportion as the number of firms by receipt category from the Census data. For example, for firms with annual receipts less than <$150,000 we divided 438 by 3,365 and multiply by 1,275 (total LDT labs) to obtain 166 (438/3,365*1,275 = 166). We repeat this calculation for the rest of the rows. We then estimate the average receipts per laboratory by receipt size category.

Table B.2 Estimated Number of LDT Laboratories and Average Annual Receipts per Laboratory (2022 U.S. dollars)

i	Enterprise Size ($1,000)	Firms	Receipts ($1,000)	Receipts IVDs Offered as LDTs Only ($1,000) in 2022 dollars adjusted for growth since 2017	LDT Labs (1,181)	Average Receipts per lab
1	< $150	438	$22,315	$12,575	166	$76
2	$151 - $499	933	$250,134	$140,954	354	$399
3	$500 - $999	413	$301,551	$169,929	157	$1,086
4	$1,000 - $2,999	481	$779,302	$439,148	182	$2,409
5	$3,000 - $5,999	343	$1,224,596	$690,078	130	$5,309

6	$6,000 - $7,999	146	$860,008	$484,627	55	$8,759
7	$8,000 - $9,999	77	$595,808	$335,747	29	$11,506
8	$10,000 - $14,999	115	$1,245,731	$701,988	44	$16,107
9	$15,000 - $19,999	79	$1,168,397	$658,409	30	$21,991
10	$20,000 - $23,999	21	$380,304	$214,307	8	$26,928
11	$24,000 - $29,999	43	$908,377	$511,884	16	$31,411
12	$30,000 - $35,999	15	$460,659	$259,588	6	$45,665
13	$36,000 - $99,999	67	$2,190,319	$1,234,278	25	$48,610
14	$100,000 +	194	$25,270,700	$14,240,421	74	$193,689
	Total	3,365	$35,658,201	$20,093,935	1,275	$15,757

We obtain the number of IVDs offered as LDTs per receipts size category in column D by multiplying column C times 79,114 (which is our estimated number of affected IVDs offered as LDTs currently on the market, as described in section II.D.1). See Table B.3.

Table B.3 Share of LDTs Offered as LDTs and IVDs Offered as LDTs per Receipt Category

i	**Enterprise Size ($1,000)**	**Percent Firms by Receipt Size A**	**LDT LABS B =Ai x 1,181)**	**Percent Receipts by Receipt Size C**	**IVDs offered as LDTs per receipt category * D**
1	< $150	13%	166	0.06%	56
2	$151 - $999	28%	354	0.70%	625
3	$1000 - $1,999	12%	157	0.85%	754
4	$2,000 - $3,999	14%	182	2.19%	1,948
5	$4,000 - $5,999	10%	130	3.43%	3,061
6	$6,000 - $9,999	4%	55	2.41%	2,150
7	$10,000 - $14,999	2%	29	1.67%	1,489
8	$15,000 - $19,999	3%	44	3.49%	3,114
9	$20,000 - $24,999	2%	30	3.28%	2,920
10	$25,000 - $29,999	1%	8	1.07%	951
11	$30,000 - $39,999	1%	16	2.55%	2,270
12	$40,000 - $49,999	0%	6	1.29%	1,151
13	$50,000 - $99,999	2%	25	6.14%	5,475
14	$100,000 +	6%	74	70.87%	63,163
	Total	100%	1,275		89,127

* Column D is the product of each row in Column C and 79,114.

The following four tables show detailed calculations leading to estimating cost as a percent of receipts using the primary, low and high estimates.

Table B.4 Detailed Calculations for Percent Receipts and Average Receipts per Lab

i	**Enterprise Size ($1,000)**	**LDT Labs**	**Receipts by Size Category**	**Percent Receipts by Receipt Category**	**Average Receipts per Lab**
	Calculation	*A*	*B*	$C_i = B_i / B_{total}$	$D = B_i / A_i$
1	< $150	166	$12,574,839	0.06%	$75,755
2	$151 - $999	327	$140,954,286	0.70%	$430,532
3	$1000 - $1,999	145	$169,928,542	0.85%	$1,172,533
4	$2,000 - $3,999	169	$439,148,446	2.19%	$2,601,807
5	$4,000 - $5,999	120	$690,078,339	3.43%	$5,733,410
6	$6,000 - $9,999	51	$484,627,495	2.41%	$9,459,407
7	$10,000 - $14,999	27	$335,746,806	1.67%	$12,425,958
8	$15,000 - $19,999	40	$701,988,231	3.49%	$17,395,652
9	$20,000 - $24,999	28	$658,409,354	3.28%	$23,750,766
10	$25,000 - $29,999	7	$214,307,047	1.07%	$29,082,108
11	$30,000 - $39,999	15	$511,884,157	2.55%	$33,924,383
12	$40,000 - $49,999	5	$259,588,303	1.29%	$49,317,674
13	$50,000 - $99,999	24	$1,234,277,833	6.14%	$52,498,495
14	$100,000 +	68	$14,240,421,072	70.87%	$209,184,656
	Total	1,193	$20,093,934,751		$16,841,846

Table B.5 Annualized Costs by Receipt Category - Primary, Low and High Estimates

i	**Enterprise Size ($1,000)**	**Annualized Cost by Receipt Category Primary, Low and High Estimates (7%)**		
	Calculation	$E_{(primary)}$ = $1,165,774,775 x C_i	$E_{(low)}$ = $510,386,965 x C_i	$E_{(high)}$ = $3,222,662,070 x C_i
1	$151 - $999	$729,545	$319,402	$2,016,751
2	$1000 - $1,999	$8,177,639	$3,580,246	$22,606,226
3	$2,000 - $3,999	$9,858,617	$4,316,194	$27,253,113
4	$4,000 - $5,999	$25,477,747	$11,154,393	$70,430,558
5	$6,000 - $9,999	$40,035,759	$17,528,025	$110,674,655
6	$10,000 - $14,999	$28,116,271	$12,309,563	$77,724,481
7	$15,000 - $19,999	$19,478,771	$8,527,986	$53,847,019
8	$20,000 - $24,999	$40,726,726	$17,830,537	$112,584,761
9	$25,000 - $29,999	$38,198,443	$16,723,631	$105,595,588
10	$30,000 - $39,999	$12,433,292	$5,443,410	$34,370,530
11	$40,000 - $49,999	$29,697,600	$13,001,884	$82,095,900

12	$50,000 - $99,999	$15,060,340	$6,593,556	$41,632,731
13	$100,000 +	$71,608,173	$31,350,720	$197,953,283
14	Total	$826,175,853	$361,707,420	$2,283,876,474
	Total	$1,165,774,775	$510,386,965	$3,222,662,070

Table B.6 Annualized Costs per Lab Receipt Category - Primary, Low and High Estimates

i	**Enterprise Size ($1,000)**	**Annualized Cost per lab by Receipt Category Primary, Low and High Estimates (7%)**		
	Calculation	$F_{(primary)} = E_{(primary)} / A_i$	$F_{(low)} = E_{(low)} / A_i$	$F_{(high)} = E_{(high)} / A_i$
1	< $150	$4,395	$1,924	$12,150
2	$151 - $999	$24,978	$10,936	$69,049
3	$1000 - $1,999	$68,026	$29,782	$188,051
4	$2,000 - $3,999	$150,947	$66,086	$417,277
5	$4,000 - $5,999	$332,631	$145,629	$919,523
6	$6,000 - $9,999	$548,799	$240,269	$1,517,098
7	$10,000 - $14,999	$720,908	$315,620	$1,992,873
8	$15,000 - $19,999	$1,009,231	$441,850	$2,789,912
9	$20,000 - $24,999	$1,377,930	$603,271	$3,809,144
10	$25,000 - $29,999	$1,687,235	$738,687	$4,664,184
11	$30,000 - $39,999	$1,968,166	$861,681	$5,440,787
12	$40,000 - $49,999	$2,861,227	$1,252,671	$7,909,561
13	$50,000 - $99,999	$3,045,766	$1,333,464	$8,419,700
14	$100,000 +	$12,136,110	$5,313,301	$33,549,002
	Total	$977,101	$427,784	$2,701,093

Table B.7 Costs as a Percent of Receipts - Primary, Low and High Estimates

i	**Enterprise Size ($1,000)**	**Annualized Cost as a Percent of Receipts per lab Primary, Low and High Estimates (7%)**		
	Calculation	$G_{(primary)} = F_{(primary)} / D_i$	$G_{(low)} = F_{(low)} / D_i$	$G_{(high)} = F_{(high)} / D_i$
1	$151 - $999	5.80%	2.54%	16.04%
2	$1000 - $1,999	5.80%	2.54%	16.04%
3	$2,000 - $3,999	5.80%	2.54%	16.04%
4	$4,000 - $5,999	5.80%	2.54%	16.04%
5	$6,000 - $9,999	5.80%	2.54%	16.04%
6	$10,000 - $14,999	5.80%	2.54%	16.04%
7	$15,000 - $19,999	5.80%	2.54%	16.04%
8	$20,000 - $24,999	5.80%	2.54%	16.04%
9	$25,000 - $29,999	5.80%	2.54%	16.04%

10	$30,000 - $39,999	5.80%	2.54%	16.04%
11	$40,000 - $49,999	5.80%	2.54%	16.04%
12	$50,000 - $99,999	5.80%	2.54%	16.04%
13	$100,000 +	5.80%	2.54%	16.04%
14	Total	5.80%	2.54%	16.04%

Table B.8 below, describes total discounted costs to industry along with the percent share of costs by stage, LDTs affected, costs per LDT along with percent affected tests, entities affected and cost per lab.

Table B.8 Discounted Costs to Industry and Percentage, by affected LDTs, by Entity and by Stage

Stage	Discounted Costs ($ Millions, 7%, 20 years)	Percent Costs	LDTs Affected	Costs per LDT	Percent Tests Affected	Entities Affected	Costs per Lab
Stage 1	$83	7%	10,013	$8,335	11%	1,275	$65,457
Stage 2	$12	1%	10,013	$1,187	11%	1,275	$9,326
Stage 3	$21	2%	52,641	$391	59%	849	$24,216
Stage 4	$361	31%	132	$2,735,305	0.1%	849	$424,763
Stage 5	$689	59%	2,446	$281,807	3%	849	$812,045
Total	**$1,166**	**100%**		**$3,027,025**			**$1,335,807**

JS 44 (Rev. 04/21) (TXND 4/21)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

American Clinical Laboratory Association, et al.

(b) County of Residence of First Listed Plaintiff Washington, DC
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*

King & Spalding LLP, 500 W 2nd Street, Ste 1800, Austin, TX 78701, (512) 457-2000

DEFENDANTS

US Food and Drug Administration, et al.

County of Residence of First Listed Defendant
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☐ 3 Federal Question *(U.S. Government Not a Party)*
- ☒ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

Click here for: Nature of Suit Code Descriptions.

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ☐ 463 Alien Detainee
- ☐ 510 Motions to Vacate Sentence
- ☐ 530 General
- ☐ 535 Death Penalty

Other:
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Management Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Employee Retirement Income Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

INTELLECTUAL PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☐ 830 Patent
- ☐ 835 Patent - Abbreviated New Drug Application
- ☐ 840 Trademark
- ☐ 880 Defend Trade Secrets Act of 2016

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 375 False Claims Act
- ☐ 376 Qui Tam (31 USC 3729(a))
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit (15 USC 1681 or 1692)
- ☐ 485 Telephone Consumer Protection Act
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District *(specify)* ☐ 6 Multidistrict Litigation - Transfer ☐ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
5 U.S.C. § 701 et seq., 21 U.S.C. § 301 et seq.

Brief description of cause:
Challenge to FDA final rule under Administrative Procedure Act

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☐ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE
05/29/2024

SIGNATURE OF ATTORNEY OF RECORD
/s/Edward F. Fernandes

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____