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December 4, 2023

VIA ELECTRONIC COMMENT

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Medical Devices; Laboratory Developed Tests
Docket No. FDA-2023-N-2177-0001

Dear Sir or Madam:

The attached comments are being submitted by Hyman, Phelps & McNamara (HPM) on behalf of the Coalition to Preserve LDT Access and Innovation (the Coalition). For the reasons set forth in these comments, the Coalition strongly opposes FDA's proposal to regulate laboratory developed tests (LDTs).

We appreciate the Agency's careful consideration of these comments as required under the Administrative Procedure Act, 5 U.S.C.§ 553.

Sincerely,

/s/Jeffrey N. Gibbs
/s/Gail H. Javitt

Jeffrey N. Gibbs and Gail H. Javitt, *on behalf of*
Coalition to Preserve LDT Access and Innovation

TABLE OF CONTENTS

I. INTRODUCTION

On October 3, 2023, the Food and Drug Administration (FDA) published a Notice of Proposed Rulemaking (hereinafter Proposed Rule)[1] to regulate Laboratory Developed Tests (LDTs)[2] as medical devices under the Federal Food, Drug, and Cosmetic (FD&C) Act. In response, Hyman, Phelps & McNamara (HPM) is submitting these comments on behalf of the Coalition to Preserve LDT Access and Innovation (Coalition), a diverse group of stakeholders including academic and commercial laboratories, health care professionals, and companies supplying laboratories with tools and materials used to perform LDTs.

We agree with FDA that diagnostic testing is essential to the health care of Americans, and that is precisely why we strongly oppose the proposed regulations. If adopted, these regulations will have the opposite effect than FDA intends; they will reduce innovation, diminish access, increase costs, and harm the care of patients, particularly those with rare diseases.[3] Moreover, FDA's proposed remedy to the purported problems with LDTs exceeds its statutory authority in multiple respects.[4]

In releasing the proposed regulation, FDA reassures readers that the Agency's proposed regulatory approach will avoid "undue disruption to the testing market."[5] This reassurance rings hollow given FDA's own projections, which show that the number of device applications by laboratories for diagnostic tests in a one-year period **would vastly exceed** the annual average of device applications the agency received between 2017 and 2021 for <u>all</u> device types. FDA struggled with a far smaller, and briefer surge in the number of Emergency Use Authorization (EUA) applications for COVID-19 tests during the public health emergency.[6] FDA does not explain how the Agency could possibly cope

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1 Medical Devices; Laboratory, 88 Fed. Reg. 68,006 (proposed Oct. 3, 2023) (to be codified at 21 C.F.R. pt. 809).

2 Throughout the Proposed Rule, FDA refers to the category of tests the Agency intends to regulate as "IVDs offered as LDTs." We will use the term "LDTs" – which is the term historically used by FDA and industry – in these comments.

3 *See infra* Section II.

4 *See infra* Section VI.

5 U.S. Food and Drug Administration (FDA), News Release, FDA Proposes Rule Aimed at Helping to Ensure Safety and Effectiveness of Laboratory Developed Tests (last updated Oct. 2, 2023), https://www.fda.gov/news-events/press-announcements/fda-proposes-rule-aimed-helping-ensure-safety-and-effectiveness-laboratory-developed-tests.

6 *See* Determination of Public Health Emergency, 85 Fed. Reg. 7,316 (Feb. 7, 2020); Guidance Documents Related to Coronavirus Disease 2019 (COVID-19), 88 Fed. Reg. 15,417 (Mar. 13, 2023).

with the expected onslaught of new, complex applications that will need to be submitted between three and a half and four years after a final rule is published.[7]

FDA's core justification for radically reshaping the regulatory landscape for diagnostics is the unequivocal and oft repeated assertion that LDTs present risks to the well-being of patients. Yet FDA, despite describing itself as a "science-based regulatory agency,"[8] fails to support its pivotal assertions with sound scientific evidence.[9] Instead, the Agency relies heavily on a mélange of anecdotes, press articles, "class-action lawsuits,"[10] internal FDA "case studies" and FDA's own, unpublished evaluation of 125 COVID-19 EUAs submitted during an unprecedented public health emergency, an entirely inapposite situation. More troubling, FDA incorrectly describes the findings of one of the two peer-review studies of clinical laboratory performance upon which it heavily relies[11] and fails to disclose a published reanalysis of the original data showing excellent overall laboratory performance by the laboratories that were the subject of the study.[12] Moreover, FDA fails to assign any benefits to LDTs, notwithstanding robust evidence that LDTs have helped to improve patient care across a wide range of medical specialties including rare diseases, oncology, maternal-fetal medicine, neonatology, new-born screening, and women's health.

There is no dispute that FDA's regulations would transform the diagnostics market in the United States. To justify this far-reaching objective, FDA makes extravagant claims for the net savings that this regulation will bring. The Agency's economic analysis, like its patient harm analysis, is riddled with supposition and error. In hypothesizing massive savings, FDA overstates the risks posed by LDTs, makes multiple assumptions about the costs associated with these risks, dramatically understates the costs that regulating laboratories as device manufacturers would impose, and completely ignores the costs of having numerous LDTs disappear due to new regulatory requirements. Given these flaws, the Agency's Preliminary Regulatory Impact Analysis (PRIA) is inadequate to support the Proposed Rule and FDA must at a minimum conduct an entirely new analysis.

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7 *See infra* Section IV(A).

8 U.S. Food and Drug Administration (FDA), Executive Summary: Strategic Plan for Regulatory Science, https://www.fda.gov/science-research/advancing-regulatory-science/executive-summary-strategic-plan-regulatory-science (current as of Mar. 29, 2018).

9 *See infra* Section III.

10 88 Fed. Reg. 68,006, 68,010 (Oct. 3, 2023).

11 *Id.* at 68,011.

12 *See infra* Section III(A).

Finally, FDA's Proposed Rule exceeds the scope of FDA's authority under the FD&C Act,[13] and is arbitrary and capricious in contravention of the Administrative Procedure Act.[14] In particular, the Proposed Rule clearly raises a "major question" for which no clear Congressional authorization under the FD&C Act is identified. To the contrary, Congress has made numerous unsuccessful attempts – partly at FDA's own request – to enact legislation to give FDA authority over LDTs, demonstrating Congress' understanding that the FD&C Act does not confer such authority. Furthermore, as discussed in greater detail in Section VI below, both the text and structure of the FD&C Act undercut the Proposed Rule's claim that the statute confers authority, by exempting health care providers (including laboratorians) who make devices for use in their practice from even the most basic device requirements, and by limiting applicability of statutory requirements to devices introduced into interstate commerce for commercial distribution, which LDTs are not.

The Coalition agrees with FDA that access to accurate, innovative diagnostic testing is necessary. For the reasons below, we believe that FDA not only lacks the legal power to issue the proposed regulations but also that these regulations, if adopted, will inflict deep harm on the U.S. healthcare system by depriving providers and patients of accurate tests that they already use and stifle innovation.

II. THE PROHIBITVE COSTS OF IMPLEMENTING THE PROPOSED RULE WILL ADVERSELY AFFECT PATIENT CARE BY LIMITING PATIENT ACCESS TO IMPORTANT DIAGNOSTICS

The imposition of device regulatory requirements on LDTs will undoubtedly result in certain diagnostic tests coming off the market. Although FDA acknowledges that some LDTs "may need to come off the market" because they "cannot meet applicable requirements"[15] this outcome is a certainty, not a mere possibility. The result will be the loss of appropriately validated LDTs that serve a critical public health need.

FDA acknowledges that over 40% of LDTs are offered by small laboratories, as it defines the term,[16] and grudgingly notes that "small laboratories . . . are more likely to

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13 FD&C Act § 201 et seq.; 21 U.S.C. § 321 et seq.

14 Administrative Procedure Act (APA), Pub. L. 79-404, 60 Stat. 237 (1946) (codified at 5 U.S.C. §§ 551–559).

15 88 Fed. Reg. 68,006, 68,014 (Oct. 3, 2023) (emphasis added).

16 The PRIA defines a small laboratory as one with annual receipts of less than $41,500,000. PRIA at 89. This definition is inconsistent with, and far more restrictive than, the small business definition for purposes of MDUFA. See https://www.fda.gov/media/93354/download (defining a small business as "having gross receipts or sales of no more than $100 million for the most recent tax year."). The PRIA provides no rationale for adopting this definition, but doing so masks the true impact of the

reduce operations or exit the market than large laboratories" if the Proposed Rule is finalized.[17] FDA's data show that almost 13,000 LDTs are offered by laboratories with receipts of less than $10 million.[18] Given the actual costs of compliance with device requirements, very few of the laboratories could afford to continue to provide these tests.[19] FDA's suggestion that some tests will vanish because "the laboratory chooses not to invest resources to meet those requirements," betrays FDA's lack of understanding of the economic realities.[20] For many laboratories, discontinuing tests will not be a choice, because they will simply not have the financial wherewithal to bear all of the costs that FDA is imposing.

Trying to downplay the adverse effects of its Proposed Rule, FDA hypothesizes that "it is possible that larger laboratories may take over the production of certain IVDs . . . ."[21] FDA offers no data to support this supposition. And even if these tests are acquired by bigger laboratories, "driving production concentration to a few large laboratories" could "increase the risk of supply chain contractions,"[22] which in turn could lead to higher prices and reduced access to tests. Furthermore, if larger laboratories do take over production of certain IVDs, the laboratories will likely run the most profitable tests, not the tests critically necessary for smaller patient populations. FDA considers the current "system of oversight as untenable and inconsistent with FDA's public health mission."[23] FDA does not explain how a revised system that will cause laboratories to close, reduce testing for rare diseases, increase market concentration, and make diagnostic testing more vulnerable to supply chain disruptions advances public health.

FDA justifies its proposal by maintaining that the current LDT regulatory regime "creates distortions in the diagnostics market."[24] Yet, FDA has no reservations about imposing a new regulatory regime that it admits will create multiple other distortions: discontinuation of many LDTs, financial harm to laboratories, concentration of tests in a small number of companies and associated increased risk of supply chain disruptions, the societal cost of fewer innovative laboratories, and higher prices for the health care

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proposed rule on small entities.

17 U.S. Food and Drug Administration (FDA), Laboratory Developed Tests Proposed Rule, Docket No. FDA-2023-N-2177: Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, Unfunded Mandates Reform Act Analysis, at 88 (Oct. 4, 2023) [hereinafter PRIA], https://www.fda.gov/media/172557/download?attachment.

18 *Id.* at 111.

19 *See infra* Section II.

20 88 Fed. Reg. 68,006, 68,014 (Oct. 3, 2023).

21 PRIA at 88.

22 *Id.* at 88.

23 88 Fed. Reg. 68,006, 68,010 (Oct. 3, 2023).

24 PRIA at 15.

system. Moreover, FDA's role is neither to set public health policy nor to address perceived distortions in the diagnostics sector.

In weighing the economic impact of its proposed regulation, FDA never discusses the loss of jobs that will occur as a result of these increased regulatory costs. Instead, FDA blithely skips over the financial harm to laboratories that go out of business or to the laboratory personnel who will lose their jobs. By FDA's own admission, 90% of laboratories that would exit the market or reduce operations as a result of the increased regulatory burden would meet the Small Business Administration's definition of a small business.[25] FDA's calculation of costs elides over the loss of employment caused by the shuttering of the laboratories.

Describing its view of the evolution of the LDT landscape, FDA focuses on the emergence of laboratories that "run their LDTs in very large volumes in a single laboratory."[26] In reality, the great majority of laboratories offer medium- and small-volume tests; roughly 75% of laboratories have revenue of under $10 million.[27] The many laboratories that are not running "very large volumes" of LDTs serve an increasingly important role in providing personalized, specialty diagnostics and tests for rare diseases. These tests generally are performed by academic medical center (AMC) laboratories and small independent laboratories. In some cases, a type of test may be offered by only a single laboratory in the United States. If the cost of FDA compliance leads that laboratory to discontinue the test or cease operations entirely, patients would lose access to the tests. This trend is particularly pronounced for tests for rare diseases and conditions. Given the limited market for these tests, it is wishful thinking to expect larger laboratories to acquire these tests and offer them at a loss.

FDA recognizes that the Proposed Rule, if finalized, may lead to a reduction in LDTs in the United States, but asserts that any such loss "may be offset by the market entry of IVDs from other manufacturers."[28] While this may be true for easily commercialized, commonly used IVDs, there is little commercial incentive for larger IVD manufacturers to offer specialty diagnostics or IVDs for rare diseases, given that there will still be substantial regulatory costs even for niche tests.

It is already well-recognized that patient populations with rare diseases are not adequately served by commercially distributed tests. For example, FDA and the National Center for Advancing Translational Sciences (NCATS)/Office of Rare Diseases Research (ORDR) at the National Institutes of Health (NIH) published a report of survey results

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25 *Id.* at 110, 112.

26 88 Fed. Reg. 68,006, 68,009 (Oct. 3, 2023).

27 PRIA at 111.

28 88 Fed. Reg. 68,006, 68,014 (Oct. 3, 2023).

from clinicians regarding unmet needs for rare diseases. Of 917 clinicians who identified unmet rare disease needs, 663 (72.3%) identified unmet *diagnostic* needs.[29] There are more than 10,000 known rare diseases.[30] Many of them are diagnosed today by LDTs; very few are diagnosed by IVDs. The dramatic increase in regulatory costs resulting from new regulatory requirements for LDTs will mean at least some of these rare disease tests will be unaffordable for laboratories to perform. It is hopelessly naïve to expect that IVD device manufacturers will fill the void. The consequence, while ignored by FDA, is completely foreseeable: clinicians and patients will lose the tools that enable the diagnosis of these rare conditions.

A recent Washington Post article regarding the potential use of artificial intelligence in the diagnosis of rare diseases cites the case of a newborn named Tess who, for the first four years of her life, had a disease that "had yet to be named or identified."[31] Laboratory results finally identified a mutation of her USP7 gene and eventually she was connected to a researcher studying the mutation and others with the same rare gene mutation. But for this LDT, it is likely that Tess's condition would not have been detected. The regulatory costs would be prohibitive for IVD manufacturers to go through the FDA process to commercialize a test for this specific mutation.

In an attempt to mitigate concerns about the loss of LDTs to address "unmet needs," FDA cites the Humanitarian Use Devices (HUD)/Humanitarian Device Exemption (HDE) program.[32] These programs, as FDA knows, are extremely unlikely to be of any assistance. Congress established these programs in 1990. In the subsequent 33 years, a total of **6 IVDs** have received an HDE.[33] Given this track record over more than three decades, it is unreasonable for FDA to expect the HUD/HDE program to provide any relief whatsoever to LDTs for rare diseases or conditions in the future.

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29 FDA & NCATS/ORDR/NIH, Unmet Medical Device Needs for Patient With Rare Diseases, at 33 (2018), https://www.fda.gov/media/111315/download; *see also* Will Greene, *Diagnosing rare diseases shouldn't be so hard*, Roche LabLeaders (accessed Nov. 2023), https://lableaders.roche.com/global/en/articles/diagnosing-rare-diseases.html.

30 NCATS/NIH, *Delivering Hope for Rare Diseases*, https://ncats.nih.gov/research/our-impact/our-impact-rare-diseases.

31 Bina Venkataraman, *Can AI solve medical mysteries? It's worth finding out.*, Wash. Post: Opinion (Nov. 15, 2023), https://www.washingtonpost.com/opinions/2023/11/15/ai-rare-disease-diagnosis/.

32 88 Fed. Reg. 68,006, 68,026.

33 U.S. Food and Drug Administration (FDA), Humanitarian Device Exemption (HDE) Database (last updated Nov. 27, 2023), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm; *see* Sandra G. Boodman, *Medical Mysteries: Dizzy and off-balance, she searched for the cause,* Wash. Post: Medical Mysteries (Nov. 25, 2023), https://www.washingtonpost.com/health/2023/11/25/unsteady-confused-incontinence-dizzy-medical-mysteries/, (LDT used on blood sample ruled out "rare, inherited and incurable brain disorder" that had been suspected as a cause of constellation of symptoms).

FDA asserts, without basis, that the new framework will help "foster" the manufacturing of innovative IVDs through "market entry of IVDs from . . . manufacturers who will have benefitted from a more consistent oversight approach and increased stability spurring innovation."[34] FDA cites no evidence supporting this hypothesis, and indeed, many of the laboratories that are creating innovative LDTs are opposed to the Proposed Rule. While it is unquestionably the case that laboratories have introduced innovative LDTs, it is sheer speculation to believe that the disappearance of these tests will accelerate innovation among IVD companies.

Indeed, IVD manufacturers use many different phrases to describe the FDA regulatory regime, but "fosters innovation" is not one. Rather, these companies' filings with the Securities and Exchange Commission (SEC) describe FDA regulation using terms such as "lengthy," "time consuming," "costly," "expensive," and "uncertain."[35] Thus, the FDA regulatory environment, in the words of IVD manufacturers, represents the antithesis of fostering innovation.

Under the proposed regulations, laboratories will not only be required to obtain an *initial* clearance or approval for their LDTs but will also be required to comply with FDA's requirements for obtaining clearance or approval of *modifications* to the LDTs (e.g., via a PMA supplement). While FDA correctly states that "a PMA supplement is required only for changes that affect safety or effectiveness" and that "a new 510(k) is only required for a significant change . . . that could significantly affect the safety or effectiveness of the device or that is a major change or modification in the device's intended use,"[36] these statements are misleading in their failure to acknowledge the myriad types of postmarket changes that trigger the need for a new submission under existing FDA regulations and guidance.[37] For example, the addition of new variants or mutations to a next-generation sequencing based IVD, or revising artificial intelligence (AI)-based algorithms to incorporate new data would each require new 510(k) clearance or approval of PMA supplements, which would reduce the flexibility and adaptability currently enabled by LDTs. The report by Pew Charitable Trust, which FDA cited multiple times, notes that "[a]ny new regulatory approach for diagnostics must be flexible enough to allow test developers to modify tests or develop new ones in order to meet

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34 88 Fed. Reg. 68,006, 68,014.

35 *See, e.g.,* Quidelortho Corp. Form 10-K, Fiscal Year Ending Jan. 1, 2023, at 41, https://www.sec.gov/Archives/edgar/data/1906324/000190632423000014/qdel-20230101.htm; Danaher Corp. Form 10-K, Fiscal Year Ending Dec. 31, 2021, at 32, https://www.sec.gov/Archives/edgar/data/313616/000031361622000061/dhr-20211231.htm.

36 *Id.* at 68,013.

37 *See* 21 C.F.R. §§ 807.81(a)(3), 814.39; FDA, Guidance for Industry and FDA Staff: Modifications to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process (Dec. 2008); FDA, Guidance for Industry and FDA Staff: Deciding When to Submit a 510(k) for a Change to an Existing Device (Oct. 2017).

patient needs without undue delay."[38] Rather than proposing this "flexible" approach, FDA has overlooked this recommendation, referencing its long-standing regulations which do not provide adequate flexibility for these necessary changes. FDA instead is seeking to shoehorn the diverse, highly innovative universe of LDTs into the existing regulatory regime.

The requirement to seek a PMA supplement for manufacturing changes will also hamper process innovation. For example, laboratories are currently nimble in being able to automate certain processes, streamline operations, or improve algorithms. These changes can reduce the cost of a test or reduce turnaround time. However, the requirement to obtain approval of a PMA supplement for process modifications is a disincentive to making changes that changes that would improve laboratory throughput or cost to patients.

FDA asserts that predetermined change control plans (PCCPs) will preserve laboratory flexibility and adaptability.[39] But PCCPs are very new, and it is not clear how well they will work or for which categories of devices. Congress authorized FDA to approve PCCPs in December 2022;[40] to date, FDA has not proposed any regulations to implement the new law, and has issued only one draft guidance on PCCPs, which is limited to AI and machine learning (AI/ML) software functions.[41] It is therefore both premature and perilous for FDA to assume that its PCCP authority will preserve laboratory flexibility. Unless and until there is an established track record, PCCPs cannot be viewed as the route for providing the flexibility that the healthcare system needs and LDTs currently provide.

FDA further seeks to mitigate the adverse impact of the Proposed Rule on patient access to testing by potentially exempting AMC laboratories from the new regulatory requirements. However, such an exemption would not address independent, non-AMC laboratories on which many patients rely. The basis for FDA's proposal is that AMC's "operate under unique circumstances (such as being integrated into direct patient care)."[42] However, non-AMC laboratories are also directly integrated into patient care, particularly with specialty diagnostics and personalized medicine. This is true, for example, in the

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38 The Pew Charitable Trusts, The Role of Lab-Developed Tests in the In Vitro Diagnostics Market (Oct. 22, 2021), https://www.pewtrusts.org/en/research- and-analysis/reports/2021/10/the-role-of-lab-developed-tests-in-the-in-vitro-diagnostics- market.

39 88 Fed. Reg. 68,006, 68,013.

40 Food and Drug Omnibus Reform Act of 2022 (FDORA), Pub. L. No. 117-328, 136 Stat. 5807.

41 FDA, Draft Guidance for Industry and FDA Staff: Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions (Apr. 2023).

42 88 Fed. Reg. 68,006, 68,023.

field of pathology. Moreover, by offering an exemption only to AMC laboratories, FDA is creating further "distortions in the diagnostics market."[43]

III. THE PROPOSED RULE PROVIDES INADEQUATE EVIDENCE OF LDT RISKS WHILE IGNORING THEIR SUBSTANIAL BENEFIT TO PATIENTS

In 2021, President Biden issued a Memorandum appointing an interagency task force to review the effectiveness of the scientific integrity policies of Federal departments and agencies and to consider, in particular, whether such policies "prevent the suppression or distortion of scientific or technological findings, data, information, conclusions, or technical results."[44] The Memorandum affirmed that the **"American public has the right to expect from its government accurate information, data, and evidence and scientifically-informed policies, practices, and communications."**[45]

The Proposed Rule fails to live up these expectations. FDA's unprecedented effort to disrupt clinical laboratory operations in the United States is premised on the Agency's assertion that patients are at risk from "unsafe, ineffective, or poor quality LDTs."[46] Commissioner Califf, in announcing the Proposed Rule, asserted that the current regulatory approach to LDTs represents "one of the most significant gaps in the healthcare system today" that "puts patients at risk."[47] To support this sweeping claim, the Proposed Rule relies on a potpourri of sources, including anecdotal reports by patients, newspaper articles, lawsuits, and FDA's assessment of the performance of LDTs during the extraordinary circumstances of the COVID-19 pandemic.

As a preliminary matter, it is surprising that a "science based" Agency would seek to build a case for regulatory regime change on class-action lawsuits and the popular press—let alone publicly admit to doing so. As FDA is well aware, a collection of anecdotal information does not constitute data.

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43 PRIA at 15.

44 Scientific Integrity Fast-Track Action Committee, National Science and Technology Council, Report on Protecting the Integrity of Government Science at 1 (Jan. 2022), https://www.whitehouse.gov/wp-content/uploads/2022/01/01-22-Protecting_the_Integrity_of_Government_Science.pdf.

45 *Id.,* Foreword (emphasis added).

46 88 Fed. Reg. 68,006, 68,010.

47 Laurie McGinley, *FDA says some lab tests are not reliable. It wants to change that.,* Wash. Post. (updated Oct. 1, 2023), https://www.washingtonpost.com/health/2023/09/29/laboratory-medical-tests-fda-regulation/.

Turning to the evidentiary record that is cited, a close review of the literature cited by FDA reveals that the Agency has presented an incomplete set of examples to justify its assertions of patient risk, leaving major gaps in its conclusions.. Conversely, in evaluating the ostensible benefits of the proposal, FDA considered only a few different medical conditions and extrapolated from them.[48] For example, FDA does not consider the costs that would arise if newborn screening were limited due to the phasing out of LDTs. It is unreasonable to extrapolate costs and benefits from only a handful of uses of LDTs. .

A. FDA's Assessment of the Risks of LDTs is Flawed

A key pillar of the Agency's harm narrative is a 2015 report submitted by FDA to Congress as part of a hearing to discuss LDT legislation.[49] The 8-year-old document created by FDA comprises 20 "case studies" that were assembled from information in FDA's enforcement action databases and other public notices. There is no context provided for the cases presented, outside of the individual cases themselves. In fact, FDA does not appear to be able to provide the appropriate public health context for this information as FDA is leveraging its "experience with non-LDT IVDs" which "gives a sense of the issues that may arise with LDTs."[50] FDA assumes that "problems may be more common because laboratories that produce LDTs may not follow key aspects of the quality system regulations, such as design controls and supplier controls."[51] Yet these case reports do nothing to establish that problems are more common with LDTs than distributed IVDs, and FDA's assertion is not supported by evidence in the Proposed Rule. FDA acknowledges this weakness in its analysis, explaining that the Agency is "limited in its ability to identify such cases as adverse events on LDTs have generally not been reported to the Agency."[52] FDA claims in the Proposed Rule that this collection of old case studies and additional evidence that they have, but will not disclose, are examples of "fundamental **uncertainty in the marketplace** about whether IVDs offered as LDTs provide accurate and reliable results."[53] A major rule that transforms the diagnostic industry cannot be predicated on "uncertainty."

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48 PRIA at 31.

49 FDA, The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies (Nov. 16, 2015), [https://web.archive.org/web/20151122235012/http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf].

50 *Id.* at 5.

51 *Id.*

52 *Id.* at 7.

53 88 Fed. Reg. 68,006, 68,010 (emphasis added).

FDA has not provided evidence that this collection of 20 individual reports establishes that LDTs are fundamentally more inaccurate or unreliable than IVDs that proceed through FDA's premarket review process. In fact, when searching FDA's recall database over a similar timeframe to that used in the referenced report—January 1, 2000 to January 1, 2015—one finds 243 *Class I Recalls* of IVDs that have undergone FDA review. Class I Recalls, are, by definition, "a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death."[54] More recently, a manufacturer of an FDA cleared lead test system recalled nearly 200,000 test kits in 2017 when it was discovered that the test system may "underestimate blood lead levels and give inaccurate results when processing venous blood samples."[55] On September 19th, 2023, the same company initiated a new recall for an error that would yield "falsely elevated results." [56] FDA's MAUDE database is replete with reports of malfunctions, serious injuries, and even deaths for IVDs that are subject to FDA regulation.

Thus, FDA's premise that costly regulation will reduce risks is undermined by evidence in FDA's own database.[57] This is not to suggest that IVDs are "problematic." However, a principal tenet of FDA's Proposed Rule is that forcing LDTs into a device regulatory regime will eliminate the costs purportedly associated with LDTs. In calculating benefits, FDA assumes that all the "harms" associated with LDTs will disappear. Yet, given that distributed IVDs also have risks, that assumption is untenable. The dichotomy that FDA has created of risk-laden LDTs and risk-free IVDs is a false one.

In effect, FDA's estimation of benefits relies on the premise that if all LDTs are replaced by IVDs, all misdiagnoses would go away. The recall and MAUDE data do not support this premise. In estimating the benefits, FDA made an error by comparing bad LDTs to a non-existent world of perfect IVDs. Indeed, in its PRIA FDA notes that IVD manufacturers need to regularly submit Part 806 notices. Thus, here FDA recognizes that IVDs do need to undergo corrections and removals, and by definition, those actions are ones that present potential health risks. However, FDA never provides an estimate for the incremental risk reduction for imposing FDA regulation on LDTs.

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54 21 C.F.R. § 7.3(m)(1).

55 Magellan Diagnostics LeadCare and LeadCare II test Kits, Class 1 Device Recall LeadCare Blood Lead Testing System, (initiated May 23, 2017) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=155436.

56 LeadCare II Blood Lead Test Kit, Class 2 Device Recall LeadCare II Blood Lead Test Kit (initiated Sept. 19, 2023), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=203593.

57 PRIA at 63.

Turning to the peer reviewed published literature—FDA places substantial weight on findings from the 2016 Diagnostic Quality Assurance Pilot, an initiative of the Sustainable Predictive Oncology Therapeutics and Diagnostics (SPOT/Dx) working group.[58] The working group was established to develop new approaches to assess laboratory test validation and performance of Next Generation Sequencing tests for oncology diagnosis and treatment. The pilot study was designed to test a method of assessing comparability of analytical performance across advanced molecular diagnostic tests. To that end, the pilot provided clinical laboratories with digital images of tissue-section slides, engineered wet-lab reference samples (the "wet-lab challenge"), and in-silico sequence data file samples (the "in-silico challenge") and developed an evaluation methodology to assess the analytical performance of validated LDTs relative to an FDA-approved companion diagnostic (CDx) for a targeted cancer therapy.

The first publication to report on the pilot data made two findings to which FDA affords significant weight in the Proposed Rule:[59]

- The accuracy of detection of genetic variants differed among the LDTs performed by different laboratories.
- The varied accuracy suggests that different LDTs may identify different subsets of oncology patients as candidates for targeted therapy.

The paper concludes that "LDTs of participating laboratories . . . may not be interchangeable with an FDA-approved CDx for identification of patients as candidates for gene-targeted therapy."

Based on its role as an observer on the pilot steering committee, FDA is well aware of the significant controversy surrounding interpretation of the pilot data. Indeed, there was a marked lack of consensus among stakeholders as to the interpretation and clinical significance of the data, as evidenced by the dissemination of a "companion discussion document" to the first publication reflecting diverse stakeholder perspectives.[60]

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[58] Jeff Allen, Naomi Aronson, Gabriel Bien-Willner et al., Implications of performance variation in next-generation sequencing-based laboratory-developed tests for oncology: Stakeholder views, Diagnostic Quality Assurance Pilot (Dec. 2021), https://www.tapestrynetworks.com/sites/default/files/publication_pdf/Diagnostic%20Quality%20Assurance%20Pilot%20-%20White%20Paper%20-%20December%202021.pdf.

[59] John D. Pfeifer, Robert Loberg, Catherine Lofton-Day et al., Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics, 157 Am J Clin Pathol 628 (2022).

[60] Jeff Allen, Naomi Aronson, Gabriel Bien-Willner et al., Implications of performance variation in next-generation sequencing-based laboratory-developed tests for oncology: Stakeholder views,

Nevertheless, FDA unequivocally claims in the Proposed Rule that the study demonstrates inadequate LDT performance. The Proposed Rule selectively presented the finding that only 7 of the 19 (37%) laboratories correctly reported all variants. Further, the PRIA broadly concludes that "among IVDs offered as LDTs, we estimate that about 47% are problematic IVDs offered as LDTs."[61] This estimate is based on the SpotDx study's finding that the analytical accuracy of 9 of 19 (47.37%) evaluated oncology LDTs was significantly lower than that of the FDA-approved companion diagnostic. However, there are a substantial number of LDTs that are approved by New York State and/or covered by Medicare, Medicaid, or Tricare, thus demonstrating the tests are not "problematic" and have acceptable sensitivity and specificity. FDA should therefore, at a minimum, subtract such tests from the 47% figure.

More troubling is the omission from the Proposed Rule of a subsequent reanalysis of the pilot data conducted by the College of American Pathologists that yielded markedly better LDT performance across multiple sites.[62] In a second publication dated September 30, 2023, the study authors reported that:

> "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 [single-nucleotide variants] was excellent, both in wet and dry engineered samples. **The overall detection rate for [single-nucleotide variants] was 96.8%.**"[63]

The authors of the reanalysis cautioned that their results "are not generalizable to all molecular oncology testing and should not be used to . . . change policy affecting all molecular oncology testing."[64] The reanalysis calls into question FDA's significant reliance on SPOT/Dx to justify wholesale regulation of LDTs. FDA must at a minimum reconsider the implications of the reanalysis for the harm proposition asserted in the Proposed Rule. FDA's heavy reliance on this study flies directly in the face of the authors' warning that the study should not be the basis for changing policy.

Diagnostic Quality Assurance Pilot (Dec. 2021), https://www.tapestrynetworks.com/sites/default/files/publication_pdf/Diagnostic%20Quality%20Assurance%20Pilot%20-%20White%20Paper%20-%20December%202021.pdf.

61 PRIA at 38.

62 Ahmet Zehir, Valentina Nardi, Eric Q. Konnick et al., SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for *KRAS* and *NRAS* Demonstrate Excellent Laboratory Performance, Arch Pathol Lab Med (2023).

63 *Id.* at 6.

64 *Id.* at 1.

FDA's presentation of SPOT/Dx is not the only instance of selective reporting of information in the Proposed Rule. A different study was described by FDA as demonstrating 70 percent discordance in laboratory test results when identical samples were sent to two different laboratories for tumor detection. However, FDA failed to mention key limitations on the findings from this investigation. Specifically, the authors acknowledged that there was a lack of control in the storage period for samples that might have affected the degree of DNA degradation and that the **"observations might not be applicable to other panels with different analytical features**." Despite this caveat in the article, FDA does precisely that, by applying these observations broadly.

As yet another example of FDA's unfounded attack on the performance of LDTs, the agency cites "one IVD offered as an LDT that delivered nine false positive results for every true cancer diagnosis."[65] As FDA well knows, the positive predictive value (PPV) of a test can be strongly affected by the prevalence of a condition. A test can have excellent performance and also be highly useful even if the PPV is approximately 10%. Although FDA cites PPV here as evidence of shortcomings in LDTs, that number, in isolation, is essentially meaningless. Indeed, FDA has permitted the marketing of multiple IVDs with PPV of 10% or less. For example, FDA approved the PMA for Cologuard, a widely used IVD for screening for colorectal cancer (CRC), with a PPV of 3.72%.[66] FDA approved a PMA for another CRC screen, Epi proColon, with an even lower PPV: 2.3%.[67] Similarly, FDA approved yet another IVD for various analytes despite having a PPV as low as 1.97% for human papilloma virus.[68] And FDA granted de novo authorization to AlloMap even though its PPV was as low as 1.8% at one time point.[69] Given that FDA has allowed IVDs on the market with PPVs of well below 10%, this "evidence" of a "problematic" LDT is meritless.

In its attack on LDTs, FDA also cites a blood test for cancer that yielded, for two separate individuals, a false positive and false negative result.[70] Again, FDA fails to provide the context of the observed events. False positive or false negative results have always and will always occur in IVD tests. In its PRIA, FDA admits that "no test is perfect 100% of the time."[71] FDA-cleared tests will inevitably result in false positive and

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65 88 Fed. Reg. 68,006, 68,011.

66 Cologuard™, Summary of Safety and Effectiveness Data, P130017, at 33 (Aug. 11, 2014).

67 Epi proColon®, Summary of Safety and Effectiveness Data, P130001, at 28 (Apr. 12, 2016).

68 cobas HPV for use on the cobas 6800/8800 Systems, Summary of Safety and Effectiveness Data, P190028, at 41 (Apr. 7, 2020).

69 AlloMap® Molecular Expression Testing, Decision Summary, DEN080007, at 15 (Aug. 26, 2008).

70 Donavyn Coffey, Blood Test Positive for Cancer, but Is There Really a Tumor?, Medscape, (updated Feb. 23, 2023).

71 PRIA at 37.

false negative results. Indeed, FDA regularly clears tests with low enough sensitivity that false negative test results are inevitable. For example, during the comment period for the Proposed Rule, FDA issued a press release touting its decision to clear a COVID-19 antigen test for at-home use with a sensitivity below 90%.[72] That does not mean that these tests are "problematic." It does mean that it is disingenuous for FDA to cite individual instances of allegedly erroneous results as evidence of a systematic problem with LDTs.

As a counter example, one major IVD manufacturer of continuous glucose meters submitted 8 Medical Device Reports for death reports in the past year and 277 MDRs reporting injury in October 2023 alone.[73] By recounting only negative outcomes for LDTs, while failing to acknowledge any negative outcomes associated with FDA regulated IVDs, FDA has conducted a fundamentally unbalanced assessment of the benefits of regulating all LDTs as devices.

FDA's "harm proposition" for LDTs also relies heavily on a New York Times article about Non-Invasive Prenatal Testing (NIPT).[74] As a threshold matter, a newspaper article does not constitute a reliable source of data regarding scientific matters. Given that, it is unsurprising that there are many flaws with the data presented in the article.

For example, the article uses the accuracy of NIPT in identifying a high-risk result to represent the overall accuracy of NIPT. Consider, for example, the 22q microdeletion (DiGeorge Syndrome), which is cited in the article. 22q microdeletion occurs in approximately 1 in 2000 pregnancies. Out of 2,000 patients, an NIPT test will return a "low risk" result for 1998 patients with near 100% accuracy. It will deliver a "high risk" result for two patients, both of whom should then proceed to have confirmatory diagnostic testing. One fetus will be affected, one will not. According to the New York Times article's logic, this means this NIPT test is wrong half (i.e., 50 percent) of the time, when in fact NIPT was wrong only 1 out of 2,000 times, or **0.05 percent**. The only way to detect 22q prenatally is to use an LDT NIPT test or to perform an invasive diagnostic test like amniocentesis. Using NIPT, only 1 in 2,000 patients will undergo amniocentesis and learn their fetus is unaffected, and there will be 100% detection of 22q in affected fetuses. Without NIPT, 22q cases would either be undetected or many unnecessary

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72 FDA, News Release, FDA Clears First COVID-19 Home Antigen Test (Nov. 9, 2023), https://www.fda.gov/news-events/press-announcements/fda-clears-first-covid-19-home-antigen-test.

73 FDA, MAUDE - Manufacturer and User Facility Device Experience Database (last updated Oct. 31, 2023), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Search.cfm.

74 *See* Sarah Kliff and Aatish Bhatia, W*hen They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong*, NY Times (Jan. 1, 2022), https:// www.nytimes.com/2022/01/01/upshot/ pregnancy-birth-genetic-testing.html.

amniocentesis procedures, with their associated risks to both the woman and her fetus, would need to be performed to detect the very small number of cases of 22q.

The New York Times article, of course, was not peer-reviewed, and there have been multiple peer-reviewed publications that came to precisely the contrary conclusion. These claims were promptly disputed. For example, one of the companies mentioned in the article clarified that its NIPT is actually greater than 99% accurate, leading the news outlet to correct its original article.[75] FDA selectively cites the original article, not the response by the company or the clarification. Nor does FDA note that professional societies have included NIPT in their guidelines. And just a month ago, yet another paper was published in the Journal of Genetic Counseling that reaffirmed, "NIPT is the best-performing screening test that can be offered in the first line for" the three principal trisomies.[76]

NIPT does not bolster FDA's argument that LDTs need to be regulated by FDA as devices. Rather, the overwhelming scientific evidence is that the NIPT being offered by laboratories is highly accurate. Subjecting them to device regulation would not lead to improved performance, but would increase cost and may well diminish availability, given the high costs of conducting prospective clinical studies for these low prevalence conditions.

When describing the need for the Proposed Rule, FDA claims that "the risks associated with LDTs are much greater today than they were at the time of enactment of the MDA" in part because modern LDTs may incorporate "high-tech instrumentation and software."[77] FDA neither provides evidence in support of this claim, nor considers the very real possibility that an automated process could reduce the risk of error that could occur during a manual process. FDA also does not consider whether high-tech instrumentation and software could confer additional benefits, such as reducing the cost or turnaround time for testing. The differences between older and newer LDT that FDA cites do not presumptively mean that modern LDTs are higher risk.

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75 Natera, News Release, Recent New York Times Coverage (Jan. 3, 2022), https://www.natera.com/company/nat-news/recent-news-coverage/; *see also* Ellen Matloff, *What The NYTimes Got Wrong On Prenatal Screening,* Forbes (Jan. 6, 2022), https://www.forbes.com/sites/ellenmatloff/2022/01/06/what-the-nytimes-got-wrong-on-prenatal-screening/?sh=18d1016137a7.

76 Adeline Perrot, Ruth Horn et al., Women's preferences for NIPT as a first-line test in England and France: Challenges for genetic counseling practices, 00 J Genet Couns 1 (Nov. 16, 2023), https://onlinelibrary.wiley.com/doi/10.1002/jgc4.1839

77 88 Fed. Reg. 68,006, 68,008.

FDA cites its experience with LDTs during the COVID-19 pandemic in support of its claim that LDTs are problematic. FDA asserts that of the "125 EUA requests for COVID-19 molecular diagnostic tests submitted from laboratories, 82 showed test design or validation problems." FDA does not describe what those problems are or how serious they were. Validation "problems" can range from potentially consequential to minor. Nor does FDA say how common "design or validation problems" were in EUAs for IVDs submitted by device manufacturers. In our experience, the rate of COVID-19 LDTs requesting authorization with sufficient validation—by FDA's estimation approximately one-third of LDT requests—is comparable to the rate we observed for EUAs submitted by IVD manufacturers during the pandemic. Nor does FDA acknowledge the numerous laboratories that were successful in obtaining an EUA. FDA has the relevant information to execute a side-by-side comparison between COVID-19 LDTs and IVD test kits and to compare the completeness of the validation between the two groups, but it is unclear that FDA conducted such analysis; certainly, the Agency does not provide it for public review. But without disclosing the rate of "design or validation problems" in IVD test kits, FDA cannot make a persuasive case that COVID-19 LDTs were comparatively deficient.

Finally, and perhaps most important, FDA does not acknowledge that COVID-19 presented a unique set of challenges that necessitated a departure from typical test development processes. At the outset of the pandemic, IVD manufacturers and clinical laboratories scrambled to submit tests to FDA. This extreme rapidity is not typical of test development for either IVD manufacturers or laboratories. Given that laboratories were racing to provide assays to meet a public health emergency, they could not have followed standard procedures for designing or validating their tests. Furthermore, FDA modified the validation requirements several times over the course of the pandemic; FDA issued 6 different EUA templates with validation standards that changed with each subsequent revision,[78] held 103 Virtual Town Halls to discuss issues related to test development,[79] and maintained a rotating set of FAQs on test development.[80] Given the exigent circumstances and departure from operational norms necessitated by the pandemic, FDA should not draw conclusions about overall LDT (or IVD) performance under ordinary conditions from EUA submissions during the pandemic.

FDA baldly asserts that LDTs present unacceptable risks, but the Agency does not know what they are. Tellingly, the Proposed Rule asserts that "FDA cannot fully assess

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78 FDA, In Vitro Diagnostics EUAs (current as of Nov. 8, 2023), https://www.fda.gov/medical-devices/covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas.

79 FDA, CDRH Learn (current as of Nov. 20, 2023), https://www.fda.gov/training-and-continuing-education/cdrh-learn.

80 FDA, FAQS on Testing for SARS-CoV-2 (current as of Nov. 8, 2023), https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2.

or address" the "the scope and scale" of "potential problems" with LDTs "without phasing out the general enforcement discretion approach for applicable requirements." The Proposed Rule acknowledges "[t]he conjectural nature of the risk reduction," but nevertheless relies on these projections to support reshaping diagnostic testing in the United States.

Rulemaking, though, is not a fishing expedition; FDA needs to justify new regulations using what is known, not on what may or may not be discovered in the future. Indeed, in the PRIA, FDA admits its lack of knowledge or references the absence of information supporting its assertions more than a dozen times. For example:

- There is a large yet **unknown** number of IVDs being offered as LDTs[81]
- Health benefits of this proposed rule, if finalized, would be the avoided costs associated with the reduction of baseline risks of known and **unknown** cases of problematic IVDs offered as LDTs[82]
- The effect of the rule on the price of IVDs offered as LDTs is **unknown**. The effect of price changes for IVDs offered as LDTs on diagnostic test usage is also **unknown**.[83]
- 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.[84]
- We **do not know** the exact number of laboratories or IVDs offered as LDTs that would be affected by this proposed rule.[85]
- We **lack the evidence** to quantify the number of tests that fall in the above categories and thus would not be affected by the proposed rule (if finalized).[86]
- We **lack the evidence** to quantify the numbers of IVDs that are within the scope of the proposed phaseout policy but for which all manufacturing activities do not occur within a single laboratory, and/or which are distributed outside of that single laboratory.[87]
- We **lack the evidence** to quantify the effect of the rule on these existing health inequities, and thus **cannot determine** whether the rule will ameliorate or exacerbate health inequity.[88]

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81 PRIA at 29 (emphasis added).
82 *Id.* at 31 (emphasis added).
83 *Id.* at 106 (emphasis added).
84 *Id.* at 18, FN 12 (emphasis added).
85 *Id.* at 21 (emphasis added).
86 *Id.* at 20 (emphasis added).
87 *Id.* at 70 (emphasis added).
88 *Id.* at 106 (emphasis added).

- **We are unable to extrapolate** this ratio to the rest of the market because: the difference in prices among currently marketed IVDs offered as LDTs and comparable other IVDs is **not known**.[89]
- **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.[90]

Before seeking to completely revamp an industry of more than 1,700 laboratories performing more than 100,000 tests, FDA needs to rely upon facts, not assumptions or speculation. Strikingly, FDA acknowledges that it does not even know the number of laboratories or LDTs.[91] It extrapolates from some CMS and New York State (NYS) data, and those estimates form the basis for all calculations about cost. It is concerning that FDA would embark on a massive revamping of the regulation of diagnostics without this most basic information: how many LDTs are there. FDA is seeking to transform laboratory regulation despite a limited understanding of the economic effects.

Relying on information about laboratories and LDTs in NYS and extrapolating from it is itself problematic. NYS has its own regulatory regime. The decision of some laboratories to locate or not locate in NYS can be affected by that unique system, and therefore, extrapolating from the state with the most unique regulatory model is itself flawed.

FDA's model for calculating the number of LDTs currently on the market uses three cases: primary, low, and high.[92] There is a 4-fold difference between high and low, and 2-fold between primary and high. Thus, FDA can easily be underestimating the cost of the Proposed Rule by a factor of 2, based on this input alone.

Notably, FDA does not address in either the preamble or the economic assessment whether IVDs that have undergone FDA review and that are then modified by labs are considered LDTs. If they are, that will have a significant impact on all cost calculations, and FDA needs to revise its economic analysis to include this large additional set of tests that would now be regulated as devices.

In short, FDA rests its claim of broad public health risk from LDTs primarily on anecdotal examples spanning more than a decade and cherry-picked findings from those few studies that have been conducted. By FDA's own admission its data are incomplete and can only serve as potential indicators of problems, meaning that these "problems"

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89 *Id.* at 52 (emphasis added).

90 *Id.* at 88 (emphasis added).

91 *Id.* at 22.

92 *Id.* at 25.

may not actually exist. FDA is unable to support any clear assertion of clinical risk that exists for LDTs under enforcement discretion or that such risk is greater than that presented by IVDs currently subject to FDA regulatory oversight. And, despite the numerous scientific publications showing that LDTs provide public health benefits, FDA does not cite a single one.

FDA's assertion that "increased oversight may help to advance health equity"[93] is similarly speculative. FDA states that:

> Some . . . LDTs have not been validated for use in all patient populations within a disease state, meaning that it is unknown how well the test may perform across diverse patient populations expected to use the test and the test may be less accurate in underrepresented patient populations, potentially contributing to health disparities.[94]

FDA does not explain why an LDT would be "less accurate in underrepresented patient populations . . . ." Furthermore, FDA-regulated IVDs sometimes include labeling statements noting that the test has not been tested in a particular patient population, so FDA regulation does not mean a test will be validated "across diverse patient populations . . . ."[95] In fact, the new requirements will directly contribute to health inequity for patients who cannot access it. The patient populations most likely to suffer are those with rare diseases or who require specialized diagnostics. FDA regulation of LDTs will result in these tests being discontinued. Regulation of these LDTs as devices will achieve health equity in the worst possible way: everyone will lose access to these tests.

B. FDA Ignored the Benefits Provided by LDTs

As described in Section II above, the Proposed Rule identifies public health and economic costs associated with LDTs, both under the current framework and if the LDTs were brought under FDA's regulation. Neither the Proposed Rule nor the PRIA ascribes even a single benefit provided by LDTs. Under FDA's view of benefits and costs of LDTs, wherein LDTs have no benefits and only costs, if one were to eliminate all LDTs from the U.S. market entirely, there would be only public health benefit. Of course, LDTs do have significant public health benefit, which highlights the flaws with FDA's incomplete analysis.

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93 88 Fed. Reg. 68,006, 68,013.

94 *Id*.

95 *See, e.g.*, Elecsys CMV IgG, Decision Summary, K220911 (Oct. 12, 2022) ("Performance characteristics have not been evaluated in immunocompromised or immunosuppressed individuals."); OraQuick Ebola Rapid Antigen Test, Decision Summary, DEN190025 (Oct. 10, 2019) ("Potential cross reactivity with Dengue Virus was not assessed.").

One of the many benefits of LDTs is the ability of laboratories to modify and adapt the LDT in response to scientific advancements or the specific needs of a patient population. In the area of cancer diagnostics, LDTs designed to detect minimal residual disease (MRD) can help clinicians determine which patients are most likely to benefit from adjuvant chemotherapy. Postoperative ctDNA status from MRD tests have also been demonstrated to be highly prognostic for cancer recurrence.[96]

As another example, the World Health Organization classification of hematolymphoid tumors has provided a global reference for the diagnosis of lymphoid neoplasms since its 3rd edition in 2001 and has been updated several times in response to scientific advances in diagnostic criteria.[97] LDTs facilitate the rapid incorporation of these new diagnostic criteria (e.g., regarding gene expression of specific subgroups that respond differently to therapy) and enable access by physicians and patients to essential information upon which to base treatment decisions. Laboratories will often launch a cancer test initially for one indication with greater prevalence and then expand the indications into other cancer types (e.g., bladder cancer). The device regulatory regime would make it much more challenging for laboratories to expand indications to reflect the latest knowledge.

The benefits of LDTs are not limited to oncology. There are numerous LDTs that are used clinically for common and rare diseases that were previously undiagnosable, and numerous publications showing that LDTs have generated improved results.

For example, LDTs play a critical role in helping prospective parents through pre-pregnancy genetic screening. Emory University has established a panel that tests for over 200 genes that are more prevalent in the Ashkenazi Jewish population[98] and Invitae offers a "Comprehensive Carrier Screen" for over 550 genetic conditions. [99] These panels enable couples to make more informed reproductive decisions. In discussing the putative, theoretical "benefits" of the Proposed Rule, FDA fails to mention the benefits these and other tests are providing today. And given the costs of the regulatory process, there can be no assurance that any laboratory or IVD manufacturer would choose to conduct the

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96 Jun Watanabe, *GALAXY: ctDNA–Based MRD May Be the Strongest Prognostic Factor for DFS in Patients With CRC, Regardless of BRAFV600E and MSI-H Status*, ASCO Daily News (Aug. 2, 2023), https://dailynews.ascopubs.org/do/galaxy-ctdna-x2013-based-mrd-may-strongest-prognostic-factor-dfs-patients-crc.

97 Rita Alaggio, Catalina Amador, Ioannis Anagnostopoulos et al., The 5th Edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms, 36 Leuk 1720 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9214472/.

98 JScreen Genetic Testing, https://www.jscreen.org/ (last visited Dec. 4, 3023).

99 *See* Invitae, Considering having a baby? Carrier screening is for you, https://www.invitae.com/us/pregnancy/carrier-screen?tab=videos (last visited Dec. 4, 2023).

thousands of separate analytical tests that would be necessary in order to navigate the FDA regulatory process for these large multi-marker panels, which include many rare conditions. If clinical data are also needed, then the costs would be significantly greater.

The benefits of LDTs continue once a baby is born. Newborn screening is widely acknowledged as one of the most successful public health programs in the country and plays a crucial role in identifying heritable conditions immediately upon birth. Each year, approximately four million newborns are screened and about 12,000 infants benefit from these life-saving diagnoses.[100] LDTs are widely used for this testing; for example, ninety percent of state laboratories screening for Severe Combined Immunodeficiency (SCID) use an LDT.[101] SCID was added to the federally recommended uniform screening panel (RUSP) in 2010 and is now screened for in all 50 states.[102] Its inclusion has proven invaluable, raising the five-year survival rate for children diagnosed with SCID to 92.5 percent - an increase of 73 percent.[103] However, an SCID test was not approved by FDA and available until 2015, fully five years after the condition was added to the RUSP.[104] LDTs filled this critical need prior to FDA approval of an SCID test, saving numerous lives, and have continued to substantially meet the demand for this test even after FDA approval. The FDA approved test is expensive for laboratories, costing approximately $6.00 per specimen, making it six times more expensive than comparable LDTs.[105] FDA's economic assessment fails to reflect that displacing LDTs can mean substantial increases in testing costs.

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[100] Centers for Disease Control and Prevention (CDC), CDC Grand Rounds: Newborn Screening and Improved Outcomes, Morbidity and Mortality Weekly Report (MWWR) (June 1, 2012), https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6121a2.htm.

[101] Ruthanne Sheller, Jelili Ojodu, Emma Griffin et al., The Landscape of Severe Combined Immunodeficiency Newborn Screening in the United States in 2020: A Review of Screening Methodologies and Targets, Communication Pathways, and Long-Term Follow-Up Practices, 11 Front Immunol. (2020), https://www.frontiersin.org/articles/10.3389/fimmu.2020.577853/full.

[102] Health Resources & Services Administration (HRSA), Summary of Nominated Conditions to the Recommended Uniform Screening Panel (RUSP) Table (Feb. 2023), https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/summary-nominated-conditions.pdf; Association of Public Health Laboratories (APHL), Newborn Screening Status for All Disorders Dashboard (last updated Oct. 30, 2023), https://www.newsteps.org/resources/data-visualizations/newborn-screening-status-all-disorders.

[103] Jess Berthold, *Newborn Screening is Biggest Factor in 'Bubble Baby Disease' Survival in Last 40 Years*, UCSF (June 20, 2023), https://www.ucsf.edu/news/2023/06/425636/newborn-screening-biggest-factor-bubble-baby-disease-survival-last-40-years#:~:text=SCID%20newborn%20screening%20enables%20earlier,%2Dyear%20survival%20to%2092.5%25.

[104] Immune Deficiency Foundation (IDF), Newborn Screening for Severe Combined Immune Deficiency (SCID), https://www.newsteps.org/sites/default/files/idf_arizonascidfactsheet.pdf.

[105] *Id.*

Newborn screening also reduces costs for patients and the health care system more broadly. The "Cost of Delayed Diagnosis" study calculated that timely diagnosis at birth of X-ALD, Pompe Disease, and SCID resulted in savings of $301,647, $168,718, and $517,638 per patient, respectively.[106]

As another example, it is standard care for pain management clinics to perform drugs of abuse testing prior to prescribing controlled substances. These clinics often establish in-house laboratories in compliance with CLIA and develop LDT-based drugs of abuse panels. LDT-based testing provides greater flexibility to develop test panels tailored to their specific patient population, which are not available from third-party manufacturers as commercial IVDs. These medical practices often serve low-income patient populations. Requiring medical clinics to adhere to standards meant for device manufacturers not only is unnecessary in light of CLIA but also would be cost-prohibitive and could result in the loss of access to pain treatment for an already at-risk, underserved patient population. Furthermore, there can be no question that the medical personnel operating these clinics are "licensed practitioners" and that the LDTs being performed in these clinics are "solely for use" with their patients in need of pain management and therefore should be exempt under 21 C.F.R. § 807.65(d).

Genetic testing is yet another area in which LDTs are already providing significant health benefits that are ignored by FDA. For example, a recent study published in JAMA Oncology evaluated RNA testing in patients undergoing hereditary cancer testing. The authors found that the use of RNA sequencing in conjunction with DNA improved both detection of variants and classification of those variants. The authors concluded, "[t]his expands the identification of individuals with hereditary cancer predisposition and increases opportunities for personalization of therapeutics and surveillance."[107] FDA's current regulatory regime is particularly ill-suited when it comes to reviewing IVDs that enable "personalization" of diagnosis.

In sum, FDA's cost/benefit analysis is doubly flawed: its calculation of costs rests on a flimsy basis and it entirely ignores the benefits that LDTs do provide.

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[106] EveryLife Foundation for Rare Diseases et al., The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study, https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf (Sept. 14, 2023).

[107] Carolyn Horton, Lily Hoang, Heather Zimmermann et al., Diagnostic Outcomes of Concurrent DNA and RNA Sequencing in Individuals Undergoing Hereditary Cancer Testing, JAMA Oncol. e235586 (2023).

IV. THE PROPOSED RULE RELIES ON A DEEPLY FLAWED ECONOMIC IMPACT ANALYSIS OF COSTS

FDA's proposed five-step, four year phaseout of LDT enforcement discretion dramatically underestimates the time and costs that will be required for laboratories to meet FDA's requirements. The Agency's assessment is set forth in its PRIA,[108] which presented estimated costs for each stage of the phaseout policy and the factors—including wages, labor hours, and personnel—that were considered in such estimates.

However, at each and every stage, the PRIA significantly underestimates the amount of time that would be required by laboratories to meet the regulatory requirements applicable to device manufacturers.

Furthermore, FDA conveniently, and euphemistically, characterizes the staggering $1.5 billion of one-time user fees that laboratories will need to pay FDA, as well as another $200 million in recurring user fees, as "transfers"—because this money is going directly from laboratories to FDA.[109] While FDA seeks to differentiate these costs from other costs imposed by the regulation by calling them "transfers", they are, from the laboratory's perspective, fees. FDA may use the term "transfers" but accountants for laboratories will call them what they are: expenses that laboratories will need to fund.

Strikingly, FDA makes the extraordinary statement that "[t]he proposed rule (if finalized) will not establish any new requirements."[110] Presumably, FDA is alluding that the medical device requirements themselves are not being altered. However, applying a panoply of regulations to an entirely new class that had not hitherto been regulated is, from the perspective of laboratories, imposing entirely new requirements.

As will be discussed in further detail below, FDA's economic analysis systematically and repeatedly either understates the costs that will be imposed or ignores them altogether. Time and again, FDA simply does not mention entire categories of regulatory requirements that will apply to clinical laboratories. In order to meet its legal obligations, FDA must redo its cost analysis.[111]

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[108] PRIA at 55-89.

[109] *Id.* at 94.

[110] *Id.* at 55.

[111] *See* Exec. Order No. 12,866, 58 Fed. Reg. 51,735 (Oct. 4, 1993) (requiring that agencies "propose or adopt a regulation only upon a reasoned determination that the benefits . . . justify its costs"); Exec. Order No. 13,563, 76 Fed. Reg. 3,821 (Jan. 21, 2011) (requiring that agencies "use the best available techniques to quantify anticipated present and future benefits and costs as accurately as possible"); *see also* Michigan v. EPA, 135 S. Ct. 2699, 2711 (2015) (holding that "the Agency must consider cost—including, most importantly, cost of compliance—before deciding whether regulation is

A. The PRIA Entirely Ignores Multiple Categories of Costs Necessary to Implement the New Requirements

Medical devices are subject to a complex set of regulations and numerous interpretive guidance documents.[112] Yet, the PRIA does not consider the additional personnel that many laboratories will need to hire to meet these requirements or the time that would be required to recruit such personnel; not a single dollar is allocated for these costs under the PRIA. Nor does FDA consider how laboratories will be able to find sufficient personnel with training and expertise in FDA regulation of IVDs, or how a surge in demand for those individuals will lead to the need to offer higher salaries and benefits. Even existing employees will still need time to review and receive training on compliance with FDA requirements applicable to device manufacturers; the PRIA does not include this personnel time in its analysis. Nor does FDA mention the expenses that will need to be incurred by laboratories in sending employees to training programs, which can cost thousands of dollars apiece.

Nor did FDA include the costs associated with Agency inspections. FDA inspections rely on different legal authorities than the regulatory bodies that currently inspect laboratories. Clinical laboratories will need to prepare accordingly, e.g., develop procedures for FDA inspections and train personnel on how to act during FDA inspections. The time spent preparing for inspections, providing information and documents to FDA during inspections, and responding to FDA observations is also substantial. FDA never mentions this time or these substantial costs. Nor does FDA acknowledge the costs imposed by uncertainty or heightened regulatory risk, or its impact on allocation of capital. Yet financial markets do take these factors into consideration, which will lead to higher costs of capital and funding for laboratories.

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appropriate and necessary."); Business Roundtable v. SEC 647 F.3d 1144, 1148-1149 (D.C. Cir. 2015) (finding the agency acted arbitrarily and capriciously because it "inconsistently and opportunistically framed the costs and benefits of the rule; failed adequately to quantify certain costs or to explain why those costs could not be quantified; neglected to support its predictive judgments; contradicted itself; and failed to respond to substantial problems raised by commenters.").

[112] *See e.g.,* FDA, Guidance for Industry and FDA Staff: Medical Device Reporting for Manufacturers (Nov. 2016), https://www.fda.gov/media/86420/download;Unique Device Identification System: Form and Content of the Unique Device Identifier (UDI) (July 2021), https://www.fda.gov/media/99084/download; Design Control Guidance For Medical Device Manufacturers (Mar. 1997), https://www.fda.gov/media/116573/download; Electronic Submission Template for Medical Device 510(k) Submissions (Oct. 2, 2023), https://www.fda.gov/media/152429/download; Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests (Mar. 13, 2007), https://www.fda.gov/media/71147/download; Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions (Dec. 2019), https://www.fda.gov/media/113230/download; Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions (Sept. 2023), https://www.fda.gov/media/119933/download.

FDA also did not include any costs for outside resources. As FDA knows from its own interactions with sponsors, IVD manufacturers routinely retain external experts, such as consultants, clinicians, biostatisticians, and attorneys, to assist with compliance and submissions. IVD manufacturers regularly spend hundreds of thousands of dollars for consulting services for marketing applications. This can be the case for even experienced IVD manufacturers. Because of their unfamiliarity with the FDA procedures, laboratories will need to draw even more heavily on external resources. The hourly costs for consultants will be materially higher than the figures FDA uses for in-house staff. For example, one consulting company, in 2019, quoted rates of $125 to $450 per hour.[113] Yet the PRIA does not include any costs related to retaining third party experts.

FDA also failed to consider the costs that will be incurred as a result of the need to comply with 21 C.F.R. Part 11. Laboratories make extensive use of software that would be subject to this regulation. As they become subject to device regulation, they will need to ensure that they now adhere to Part 11, and that migrating to Part 11-compliant systems does not disrupt ongoing operations. This will require support by trained software engineers. The PRIA never mentions the time or costs of migrating to Part 11-compliant systems.

The Proposed Rule states that FDA plans to issue "more targeted guidance" and may make available additional compliance resources, e.g., relating to labeling, over the course of the phaseout period.[114] However, laboratories will need to receive this guidance in a timely manner in order to ensure they are appropriately implementing the final rule. Laboratories that initiate implementation of these requirements before such guidance is issued may need to expend additional time and resources to redo their processes. Furthermore, the guidance may lead to additional submissions, documentations, or other changes to comply with the guidance recommendations, yet the economic assessment does not factor in these marginal costs of compliance.

B. FDA Significantly Underestimates the Costs of Each of Its Phases

The deficiencies in FDA's PRIA assumptions are evident at every stage of the proposed phaseout. Given the huge number of individual tasks that FDA has identified, we will provide only representative examples here. Stage 1 would require laboratories to be in compliance with the Medical Device Reporting (MDR) [115] and correction and removal[116] regulations one year after the final phaseout policy is implemented.[117]

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[113] Robert Fenton, *How Much Does Medical Device Regulatory Consulting Cost in 2020?*, Qualio (Dec. 24, 2019), https://www.qualio.com/blog/medical-device-regulatory-consulting-cost.

[114] 88 Fed. Reg. 68,006, 68,024.

[115] 21 U.S.C. § 360i(a)-(c); 21 C.F.R. Part 803.

[116] 21 U.S.C. § 360i(g); 21 C.F.R. Part 806.

Consequently, laboratories will need to begin allocating resources toward Part 803 and Part 806[118] compliance as soon as a final rule is published.

In the PRIA, FDA acknowledges that laboratory standard operating procedures (SOPs) will need to be modified to incorporate requirements for MDR reporting and estimates that such modification will require a maximum of 36 hours.[119] FDA's estimate assumes that laboratories will already have relevant SOPs in place and that management personnel – and presumably other staff – will be familiar with MDR requirements. Neither of these assumptions will be correct for most laboratories. Given that laboratories have not been subject to MDR requirements, they will essentially have to construct entirely new procedures that comply with this regulation that are crafted to address the needs of their facility. In addition to reviewing and mastering the MDR regulation itself, laboratory staff will need to review and incorporate the various guidance documents FDA has developed, such as the 46-page guidance document issued in 2016.[120] Laboratory personnel will need to schedule meetings to discuss, review, and approve the new SOPs, which will likely exceed 36 hours in total. Nor does FDA's estimate account for the time needed to train all the relevant personnel on the new SOP, such as Regulatory Affairs, Quality Assurance, and staff receiving and assessing complaints. Creating, implementing, and training personnel on compliance with new SOPs will take far longer than 36 hours to complete. FDA's estimates are wholly unrealistic.

Nor does FDA acknowledge the substantial time that laboratories already must spend preparing and maintaining SOPs under CLIA; one laboratory member of the Coalition that is accredited by CAP estimates a minimum of 100 hours to create and implement training and personnel SOPs and in excess of 70 hours annually to maintain

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[117] The Proposed Rule states that the final phaseout policy will be published in the preamble to the final rule. 88 Fed. Reg. 68,006, 68,023.

[118] As discussed in Section VI(C), *infra* pp. 53-57, Part 806 requirements are premised on the assumption that a product enters commercial distribution, which LDTs do not, further demonstrating the fundamental unsuitability of the device regulatory framework for LDT oversight. *See* 21 C.F.R. § 806.2(h) ("Manufacturer means any person who . . . [r]epackages or otherwise changes the container, wrapper, or labeling of a device *in furtherance of the device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user or consumer . . . [i]nitiates specifications for a device* that are manufactured by a second party for subsequent distribution by the person initiating the specifications . . . [or] [m]anufactures components or accessories that are . . . intended to be . . . commercially distributed . . . ." (emphasis added)). LDTs are not commercially distributed, delivered, nor sold to an ultimate consumer or user.

[119] PRIA at 58.

[120] FDA, Guidance for Industry and FDA Staff: Medical Device Reporting for Manufacturers (Nov. 2016), https://www.fda.gov/media/86420/download.

certification and comply with reporting obligations. The MDR requirements will be additional to these already applicable CLIA obligations.

Indeed, a pervasive flaw in the PRIA is FDA's failure to adequately account for ongoing compliance costs. As one example, FDA grossly underestimates the costs to maintain compliance with the MDR requirements. FDA states: "Finally, we expect a recurring cost associated with filing and submitting MDRs. We estimate it will take computer and information system managers 430 hours . . . .".[121] Strikingly, FDA's estimate never mentions all of the other personnel who will need to be involved, such as Regulatory Affairs, Quality Assurance, and Clinical Affairs. In fact, FDA's time and cost assessment is static; it does not account for the fact that most laboratory personnel are already working at 100% bandwidth. Therefore, more regulatory burden means that laboratories will be required to hire more personnel. Every 35 hours of time to comply with FDA regulations is another person-week of work, and there is limited supply of qualified employees in this specialized field.

In order to comply with the regulation, these personnel must evaluate and draft MDRs. By referencing only "computer and information system managers," FDA ignores all of the other staff who will be involved in the submission of an MDR. FDA also ignores all of the time that must be spent to determine whether an event needs to be reported in the first instance. Once laboratories are subject to the MDR regulation, they will need to evaluate certain reports to determine whether an MDR is needed and to prepare documentation justifying decisions not to file an MDR, and, if one is not, document that decision.[122] IVD manufacturers currently receive many complaint reports that, after evaluation, are determined not to meet the standard for reporting to FDA per the MDR regulations. The need to conduct these evaluations and document decisions not to report will take significant time and impose costs upon laboratories, but FDA does not include this under the PRIA.

Managing quality data and conducting MDR evaluation also will require laboratories to modify existing software platforms or adopt new ones. And these changes will need to be done in accordance with 21 C.F.R. Part 11, which will make them more time-consuming and costly. FDA did not include the time or personnel needed for this step. Nor did FDA account for the need for employee training following the implementation and validation process.

Regarding correction and removal reporting, the PRIA analysis appears to assume that laboratories already have an equivalent process in place and that generating a report will be the only additional step laboratories need to implement. However, laboratories

[121] PRIA at 60.
[122] 21 C.F.R. § 820.198(a)(3).

will not have processes for complying with this regulation. There has never been a need for laboratories to develop procedures to meet the requirements of this very specific regulation. Although CLIA regulations do require complaint investigation,[123] Part 806 includes many additional elements that will be new to laboratories, and laboratories will need to create entirely new procedures, and then train personnel. The PRIA does not include this cost.

With respect to ongoing costs, FDA once again grossly underestimates the time and personnel involved. FDA "assume[s] it will take a single general/operations manager . . . 10 hours to create a single correction and removal report."[124] Drafting Part 806 reports, however, is not the work of a single individual. Part 806 lays out a long list of items that must be provided to FDA.[125] In order to submit a Part 806 report, companies must draw upon the expertise of Clinical Affairs, Regulatory Affairs, Quality Assurance, and Operations, and may also engage external resources.

Once again, FDA's cost estimates are also substantially flawed because the Agency considers only what is submitted pursuant to Part 806 and disregards all the work that must be done to determine whether a report must be submitted in the first instance. Under Part 806, companies must regularly evaluate and determine whether a report needs to be submitted, and then document that decision.[126] The failure to do this is subject to enforcement action. In our experience, these evaluations that determine a report is not needed are more common than ones resulting in the need to submit a report. Conducting these assessments, which may involve performing a multi-disciplinary Health Hazard Evaluation and consulting with counsel, can be labor intensive.[127] FDA's estimate of recurring costs totally ignores the requirement to conduct these assessments.

Turning to Stage 2, FDA expects laboratories to be compliant with registration and listing,[128] labeling,[129] and investigational use requirements[130] two years after publication

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[123] 42 C.F.R. § 493.1233.

[124] PRIA at 62.

[125] 21 C.F.R. § 806.10(c).

[126] 21 C C.F.R. § 806.20.

[127] FDA, Health Hazard Evaluations (HHEs) and Health Risk Assessments (HRAs) (current as of Dec. 19, 2017), https://www.fda.gov/about-fda/cdrh-transparency/health-hazard-evaluations-hhes-and-health-risk-assessments-hras.

[128] 21 U.S.C. § 360 and Part 807 (excluding subpart E).

[129] 21 U.S.C. § 352 and Parts 801 and 809, subpart B.

[130] 21 U.S.C. § 360j(g) and Part 812.

of the final phaseout policy. The PRIA assumes that each affected laboratory will initially register a single establishment and list an average of 67 products.[131]

The 3-hour estimate appears to relate solely to the time for technical data entry necessary to complete the registration and listing process and does not consider the work that needs to be done in advance of entering the data.

FDA's failure to include the time needed for preparation prior to data entry is similarly seen with respect to device registration and listing. The PRIA does not take into account the additional time needed to use the Device Registration and Listing Module (DRLM) within the FDA Unified Registration and Listing System (FURLS). This process involves entering regulatory information for each device, including medical specialty, product code, device/product name, class, and premarket submission number (optional). The PRIA appears to further assume that a general/operations manager within a clinical laboratory will already be adept at using this specialized platform, but this assumption is unfounded. Even experienced regulatory personnel can have difficulty navigating this system.

Furthermore, laboratory personnel will need to conduct regulatory research to determine the correct information to enter, which in turn requires an in-depth understanding of the intended use of the tests, FDA regulations and classifications for IVDs, existing classification regulations, and determining an appropriate classification for each test. Laboratories will need to train these managers on use of the FURLS system and DLRM module or to hire regulatory affairs personnel or outside consultants to complete these tasks within the two-year deadline. The 3 hour estimate for the initial registration and listing and the 1-hour estimate for the annual renewal of registration and listing overlooked all of the substantial time required to research and compile the required information, and included only the final data entry step.

Neither the Proposed Rule nor the PRIA clearly defines the scope of who is a "manufacturer." Instead, the Proposed Rule uses "manufacture" and related terms as a shorthand for the various activities that constitute manufacturing as described in FDA regulations (e.g., design, preparation, propagation, assembly, and processing).[132] It is unclear if FDA will consider any entity that helps a laboratory design a test to be a "manufacturer" and therefore subject to registration and listing. If so, it is also unclear if FDA included all of these entities that perform design, preparation, propagation, assembly, or processing in its cost and scope estimates for the Proposed Rule. If FDA does view these entities as manufacturers that must register, then FDA must adjust its cost estimates accordingly.

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[131] PRIA at 59.

[132] 88 Fed. Reg. 68,006, 68,008.

Concerning labeling compliance, the PRIA estimates 4-34 hours of general/operations manager time[133] to redesign "existing labeling"[134] to meet applicable medical device labeling requirements.[135] Of course, laboratories issue laboratory test reports, not labeling, and so there is no "existing labeling." FDA's IVD labeling regulation is extremely complex, containing up to 45 separate elements[136]. Converting laboratory reports to compliant IVD labeling is not a trivial task. Moreover, because laboratories will need to draw upon multiple disciplines and experts, such as Regulatory Affairs, Quality Assurance, and Technical Support, completing the task will take many individuals beyond a general/operations manager. Laboratories will need to develop procedures for labeling controls. FDA's cost estimate, by assuming that all of this work can be done by one person, is fundamentally flawed. Moreover, FDA does not address the issue of how the laboratory reporting obligations of a Laboratory Director under CLIA can be squared with FDA's prescriptive labeling requirements.[137]

Moreover, it is unclear whether this estimate is for a single test or for all of a laboratory's tests combined (which FDA estimates at 67 tests per laboratory, as noted above). If the estimate is for a single test, then the time required to redesign labeling for 67 IVD products offered as LDTs per laboratory would be far greater: 268- 2,278 hours, or up to 56.95 weeks. In other words, a general/operations manager would need to devote more than a year of time exclusively to labeling redesign, during which time they would be unable to focus on address registration, listing, investigational use requirements, or other aspects of their current role.

On the other hand, if FDA's 4-34 hour estimate is for the aggregate time needed to revise labeling for 67 tests, this means a general/operations manager would be spending only 0.06 to 0.5 hours—or about 4-30 minutes) per test, which is a wholly unrealistic estimate of the amount of time required to become familiar with the labeling regulations and then draft compliant labeling for a specific test. As FDA knows from its reviews of IVD labeling, they can be voluminous, complex documents.

The PRIA also fails to mention the specific time and cost necessary to comply with the labeling requirements for unique device identification (UDI). The original rollout of this process was extended multiple times over almost 10-years after publication of the final rule, in part because of the challenges in implementing. Established device

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[133] PRIA at 65.

[134] *Id.* at 66.

[135] 21 U.S.C. § 352; 21 C.F.R. Parts 801 and 809, subpart B.

[136] This reflects 10 points under subpart (a) for the label, 15 points under subpart (b) for the package insert, 9 parts under subpart (d)(1) for general purpose reagents, and 11 points under subpart (e)(1) for analyte specific reagents.

[137] 42 C.F.R. § 493.1407.

manufacturers with experience in all other device regulations were given a minimum of two years, with many device classes having more than five years to comply. It is unreasonable to think that each lab will be able to establish UDIs for all LDTs in addition to all other labeling requirements within two years. Unless FDA believes that the UDI regulation is inapplicable to LDTs – which, if that is the case FDA should affirmatively say to remove any ambiguity – the revised economic analysis needs to include these costs as well.

Regarding compliance with the investigational device exemption (IDE) requirements,[138] the PRIA does not factor into its analysis the time and cost required to implement design controls for LDTs used in clinical investigations.[139,140] Although most aspects of the quality system regulation (QSR), 21 CFR Part 820, do not go into effect until Stage 3, laboratories seeking to conduct clinical investigations with LDTs would in fact be subject to this QSR provision a year earlier, which would give them even less time to implement design control procedures or establish design history files[141] as required by Part 820. As many laboratories foreseeably will need to conduct clinical investigations of their LDTs to submit marketing applications in Phases 4 and 5, the requirement for design controls will be widely applicable.

With respect to other aspects of QSR, the proposed rule would require compliance three years after publication of the final phaseout policy."[142] The elements of QSR applicable to an LDT would depend on whether all manufacturing activities take place within a single laboratory and there is no distribution outside the laboratory. Even in that limited case, compliance would be required for design controls,[143] purchasing controls (including supplier controls),[144] acceptance activities (receiving, in-process, and finished device acceptance),[145] corrective and preventative actions (CAPA),[146] and records requirements.[147] Otherwise, all elements of QSR would be applicable.

The PRIA developed an estimate of the one-time and recurring annual amount of labor hours required for most sections of the QSR. Additionally, FDA computed the

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[138] 21 § U.S.C. 360j(g), 21 C.F.R. Part 812.
[139] 21 C.F.R. § 820.30.
[140] 21 C.F.R. § 812.1(a).
[141] 21 C.F.R. § 820.30(j).
[142] 88 Fed. Reg. 68,006, 68,024.
[143] 21 C.F.R. § 820.30.
[144] 21 C.F.R. § 820.50.
[145] 21 C.F.R. §§ 820.80, 820.86.
[146] 21 C.F.R. § 820.100.
[147] 21 C.F.R. Part 820, subpart M.

primary estimate by averaging these two estimates. Although FDA specified the number of hours for many provisions of the QSR, the factors that were considered to derive these numbers, such as the split between different types of personnel and amount of time to be spent on the various aspects of compliance, was not provided.[148] For example, purchasing and supplier controls require input from legal and finance personnel, who are involved in negotiations with suppliers, in addition to regulatory personnel. Developing and negotiating Quality Agreements with suppliers can be a major, time-consuming undertaking by itself. This requirement, which FDA has imposed on IVD manufacturers, is not reflected in the PRIA.

Nor does the PRIA include the time needed for laboratories to select, implement, and validate software platforms for QSR compliance, which are widely used by in vitro diagnostic device manufacturers, or, alternatively, to adapt existing systems to include QSR compliance capabilities. The PRIA allots 0-40 hours for initial compliance with 21 C.F.R. § 820.70(i) (Automated Processes). However, implementing software platforms requires subject matter experts across multiple disciplines, including Information Technology, and typically takes months. Companies routinely need to hire outside software experts; these costs are omitted, as are software license fees. An estimate of 40 hours (approximately one week for one full-time employee) is far too low for this activity. This also disregards the need for the work to be done in accordance with Part 11.

The PRIA also does not account for the initial time and cost needed for laboratories to develop design history files for existing tests, as required by 21 C.F.R. §820.30(a), or for the recurring time and costs for design planning,[149] design review,[150] design verification,[151] design transfer,[152] and design change[153] activities and establishing the design history file.[154] The PRIA omits all mention of design input,[155] design output,[156] and design validation/risk analysis. Some LDTs have been on the market for a decade or more, and document retention policies mean that contemporaneous documents may have been lost to history. Recreating design documentation retrospectively is incredibly time consuming and costly.

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[148] PRIA, Table 23.
[149] 21 C.F.R. § 820.30(b).
[150] 21 C.F.R. § 820.30(e).
[151] 21 C.F.R. § 820.30(f).
[152] 21 C.F.R. § 820.30(h).
[153] 21 C.F.R. § 820.30(i).
[154] 21 C.F.R. § 820.30(j).
[155] 21 C.F.R. § 820.30(c).
[156] 21 C.F.R. § 820.30(d).

It is therefore not clear whether laboratories will be expected to develop DHFs for existing tests during Stage 3 or, rather, will be expected to implement this requirement prospectively only. Establishing a separate DHF for 67 LDTs will be incredibly labor intensive and will require input from individuals with scientific, technical, clinical, and regulatory expertise, some of whom may need to be hired. If the laboratory personnel who initially developed a test are no longer with the organization, additional time to investigate the design of the test will be necessary (e.g., reverse engineering software code to determine its requirements and architecture). Even established companies with expertise in design controls require many months to develop a DHF. Considering labs will be new to the process and the estimate that, on average, each lab will have 67 tests, three or even four years to come into full compliance with design controls is not attainable and will cost far more than estimated.

FDA's other estimates for QSR compliance are absurdly low. A few examples suffice to make the point. FDA states that the Quality Audit will take one hour per year.[157] In actual fact, IVD manufacturers may take dozens of hours a year simply to schedule and plan quality audits. Addressing audit findings itself may take significant resources. A company that spent one hour a year on its quality audits would be deemed derelict by FDA. FDA's own Quality System Inspection Technique[158] allows one day per subsystem for a total of four days to review an entire quality system.

FDA also states that Management Review will take eight hours a year.[159] FDA appears to assume that management review will consist of roughly four individuals, who meet once a year for two hours, and that no preparation time is needed for the meeting. All of those assumptions are wrong. Management review can involve far more than four individuals, occur more frequently – some IVD manufacturers hold them monthly – and require substantial time to prepare the materials that management reviews. FDA's cost estimates for this element alone will be two orders of magnitude too low for some laboratories.

FDA also estimates that 2 to 4 hours would be needed for records, which must assume one or two complaints per year. FDA's QSR costs estimates dramatically understate the actual costs that will be incurred and are inconsistent with regulatory obligations.

In its "Low" estimates, FDA inexplicably and without explanation lists zero hours for multiple QSR elements, including Quality Audit, training, identifying training needs,

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[157] PRIA at 72.

[158] FDA, Guide to Inspections of Quality Systems, Quality System Inspection Technique (Aug. 1999), https://www.fda.gov/files/Guide-to-Inspections-of-Quality-Systems.pdf.

[159] PRIA at 72.

and document controls.[160] A laboratory that spent zero hours on those activities would be either grossly non-compliant or defunct.

Turning to Stages 4 and 5, laboratories performing high-risk (Class III) LDTs will need to submit a PMA within 3 1/2 years of finalization of a final phaseout policy,[161] while laboratories offering low and moderate risk (Class I and II) LDTs will need to submit applications within 4 years of FDA publishing a final phaseout policy.[162]

FDA asserts that "3 1/2 years would provide sufficient notice and opportunity for laboratories manufacturing IVDs to plan for and prepare PMAs and would appropriately account for any reliance interests."[163] FDA's reasons for allowing an extra six months for moderate and low risk LDTs is to prioritize the higher risk submissions.[164] However, FDA's assertions are flawed.

For example, no prudent laboratory would simply generate data to support a PMA, De Novo, or 510(k) application. Rather, just as is the case for IVD manufacturers now, laboratories would need to spend a significant amount of time (1) developing a regulatory strategy; (2) drafting protocols, analytical study plans, intended uses, and statistical plans; (3) submitting these to FDA through the pre-submission process and awaiting feedback;(4) modifying the plans to accommodate FDA's comments; (5) potentially submitting a second pre-submission to obtain concurrence in the plans; (6) developing SOPs and infrastructure, including software, to manage the clinical study and data; (7) hiring internal staff and Contract Research Organizations to develop and execute the study plans; (8) locating potential investigational sites; (9) negotiating clinical trial agreements with the sites and auditing the sites to determine suitability and obtaining Institutional Review Board approval for the sites; (10) conducting the study in accordance with Good Clinical Practices, including site audits; (11) obtaining and verifying all study data; (12) analyzing the data in accordance with the statistical plan; (12) conducting all analytical studies, many of which will be done at third party laboratories; and (13) drafting a multi-volume submission including all of this information. Each laboratory will need to do this simultaneously for each test. This will inevitably mean delays in obtaining feedback from FDA regarding pre-submissions and other questions, and a shortage of qualified CROs, biostatisticians, clinical research associates, clinical sites, Directors of Clinical Affairs, and other personnel. There are a finite number of "true positives" in a year for a given disease, particularly rare diseases,

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[160] *Id.*, Table 23.
[161] 88 Fed. Reg. 68,006, 68,024.
[162] *Id.*
[163] *Id.* at 68,026.
[164] *Id.* at 68,027.

and LDTs targeting the same clinical application will be in competition for these true positives in order to run adequately powered studies.

The Proposed Rule blithely ignores all of these challenges. The effect is that, in order to meet the 3 ½ or 4-year deadline for submission of all marketing applications, laboratories will need to start work on their submission strategies virtually the day after the regulation is finalized. They will need to do all of this work while concurrently developing and implementing procedures for MDRs and Part 806 reporting, registering and listing, revising test labeling, and revamping their systems to meet QSRs. They will need to do this with staff that has limited to no familiarity with the FDA device regulatory regime.

FDA also fails to take into account the actual costs associated with the experts that laboratories will need to engage; for example, one outside group at a non-profit organization charges $190/hour for "biostatistical support/data analysis."[165] This is notably higher than the rate used by FDA for other staff identified in the PRIA. Given that laboratories do not generally have biostatisticians on staff, they will need to rely on external resources.

FDA's proposal also ignores yet another issue, namely, the need to determine the appropriate type of marketing application, which is not always self-evident. FDA does not lay out a mechanism for gaining that information. While the Agency states that laboratories may "work with FDA to determine whether PMAs should be submitted for their IVDs,"[166] FDA does not describe how this will be done, how long it will take, or what expenses a laboratory will incur in getting this feedback. Thus, companies may proceed in good faith in the belief that their LDT is a Class II device, only to be told that it is actually Class III and they are out of compliance. Without a clear, efficient procedure for determining classification for these LDTs, it is inevitable that this situation will occur repeatedly.

Indeed, one of the underlying assumptions in the Proposed Rule appears to be that since laboratories will be subjected to already-existing FDA regulations, their transition to device regulation should be straightforward. As noted throughout these comments, that assumption is wrong; there are multiple areas of ambiguity and uncertainty related to the application of these existing rules to the clinical laboratory environment, which will increase costs for laboratories and put additional strains on FDA as the Agency works to provide clarity to both the entire laboratory industry and individual companies.

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[165] Arizona State University Biostatistics Consultation Core, Services and Fees, https://chs.asu.edu/biostatistics/services (last visited Dec. 4, 2023).

[166] 88 Fed. Reg. 68,006, 68,026.

For 510(k)s, FDA also underestimates the time required to identify a suitable predicate device for an LDT. Conducting a predicate search is a complex process with significant regulatory ramifications. As FDA well knows, selecting the "wrong" predicate can greatly complicate the regulatory process for applicants. Regulatory affairs professionals have informed us that it can take over 10 hours to identify the correct predicate for some simple submissions, and many LDTs will not be simple. Yet the PRIA estimates 1-2 hours for a single operations specialist manager – who presumably has no regulatory affairs experience – to identify a predicate device or determine that no predicate exists.

Device manufacturers frequently use the Q-Submission process for this purpose. However, it is important to note that FDA will face resource constraints if a high volume of pre-submissions flood in, especially considering that nearly every laboratory will need to submit a pre-submission before submitting a premarket submission and some labs may submit multiple pre-submissions to address different types of tests (recall that FDA estimates each laboratory has 67 LDTs). In 2021, during the second year of the COVID-19 pandemic, CDRH announced its declination of IVD pre-submissions that were not related to COVID-19, companion diagnostics, or a breakthrough designation request, or those that did not have a significant public health impact.[167]

Under FDA's own forecasts, the influx of pre-submissions by laboratories will be even worse. Using the PRIA's "primary projection for LDT applications, the number of device applications by laboratory tests would exceed the annual average of device applications the agency received between 2017 and 2021 for all device types by a factor of 10.[168] Moreover, applying the "high" projection, the Agency expects to receive approximately **20 times more** LDT applications in one year than it normally receives across all device types. Worse still, FDA projects that a disproportionate share of these LDT applications will be PMAs and requests for de novo classification—which are the more time-intensive applications for sponsors to assemble and for FDA to review. Specifically, FDA projects that it will receive fifty-seven-times more PMAs than it normally receives in a year and sixty-one-times more de novo requests than it normally receives in a year (using FDA's "primary" model). Nor will this be a one-time phenomenon; a number of LDT applications FDA projects receiving on an ongoing basis will at least double the total number of applications received annually across all of CDRH.

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[167] *See* Jeff Shuren & William Maisel, A Year Into the Pandemic: How the FDA'S Center for Devices and Radiological Health is Prioritizing its Workload and Looking Ahead, FDA Voices (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

[168] PRIA, Table 4 at 28.

Based on the COVID-19 experience, it is predictable that the pre-submission process will be a bottleneck. Yet FDA's proposal sets firm deadlines for submission of applications, with no delays due to FDA's own inability to provide feedback on pre-submissions. These same problems would occur for 510(k) and de novo submissions.

In short, the PRIA and proposed phaseout timeline allocates insufficient time and significantly underestimates the cost at each Stage. FDA ignores the innumerable steps needed to comply with FDA regulatory requirements applicable to device manufacturers. The foreseeable net effect of imposing these requirements will be that many LDTs will be discontinued. The PRIA gives no consideration at all to the costs that patients and society will incur as a result of these tests becoming unavailable.

In both the preamble and the PRIA, FDA repeatedly asserts that the benefits of regulating LDTs will substantially exceed the costs. Yet, a closer look at FDA's own figures shows that such an outcome is not assured. FDA states that the benefits could be as low as $2.67 billion, while the costs could be as high as $19.45 billion.[169] For the reasons given above, FDA has both overestimated benefits and underestimated costs. Even within FDA's own flawed economic analysis, imposing this highly disruptive regulatory change may cost roughly $17 billion more than it saves. In discussing the Proposed Rule, FDA never addresses this possibility, which is laid out in its projections. FDA states unequivocally that regulating LDTs as devices will provide benefits, although it also repeatedly acknowledges the uncertainties regarding the size of those benefits. Those statements fail to acknowledge the extraordinary uncertainty in FDA's projections. Using a 7% discount rate, FDA estimates that the benefits over 20 years could range from $2.67 billion to $86.01 billion.[170] The fact that FDA's projected benefits vary by a factor of 32 is itself evidence of the extreme uncertainty in these projections. However, given FDA's repeated acknowledgement that it lacks information on key inputs and its repeated use of speculation and extrapolation, it is not surprising that the difference between the high and low projections would be so widely divergent.

Finally, the claim that benefits outweigh costs entirely ignores one important element: the benefits that LDTs provide. Those benefits are jeopardized by the imposition of the device regulatory regime. In looking at the economic impact of LDTs, FDA must consider the benefits they provide and the costs that would be imposed if, for example, there are no longer tests for patients with rare diseases or conditions. The failure to adequately assess the economic impacts of a rule violate the APA.[171]

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[169] 88 Fed. Reg. 68,006, 68,008.

[170] *Id.*

[171] *See, e.g.,* Chamber of Commerce of United States v. United States SEC, 85 F.4th 760 (5th Cir. 2023). The Court found SEC's rule arbitrary & capricious because the SEC solicited information to help

V. EXISTING REGULATORY FRAMEWORKS ARE ADEQUATE TO ENSURE SAFE AND EFFECTIVE TESTS

LDTs are currently subject to regulation under the Clinical Laboratory Improvement Amendments (CLIA).[172] Enacted in 1988 for the purpose of ensuring that laboratories provide safe, accurate, and timely results to patients, CLIA vests broad authority in HHS to implement regulations that ensure the quality of clinical laboratory testing. Congress viewed CLIA as the federal statute that was sufficient to ensure the performance of laboratory tests. There is no reference to any role for FDA in the legislation.

Under CLIA, laboratories are required to become certified either directly by an agent of the Centers for Medicare & Medicaid Services (CMS), or via an accreditation organization approved by CMS (e.g., the College of American Pathologists [CAP]). To obtain a CLIA certificate, a laboratory must demonstrate that the personnel in the laboratory have the training, experience, and level of proficiency required to perform the types of tests offered by the laboratory. CLIA-certified laboratories are subject to inspections to confirm that the testing complies with CLIA regulations, including ensuring that there is adequate validation of the tests, supervision by the laboratory director, and quality procedures.

To the extent improvements are needed to CLIA requirements, the existing regulatory framework should be the vehicle for improvements. For example, the Clinical Laboratory Improvement Advisory Committee (CLIAC), managed by the Centers for Disease Control and Prevention (CDC), provides scientific and technical advice and guidance to the Department for Health and Human Services (HHS) regarding "improvement in laboratory quality and laboratory medicine practice.[173] CLIAC includes three members from federal agencies that oversee the CLIA program, including a member from FDA. CLIAC has provided advice and guidance to HHS on revisions and improvements to the CLIA standards. CLIAC's recommendations to HHS is a more suitable avenue for improvements to laboratory regulation.

Many states also have laboratory laws requiring separate state licensure, inspection, and compliance with additional quality and documentation requirements. These state laws provide supplemental laboratory requirements beyond CLIA

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quantity the costs and benefits of the rule and then ignored it after it was provided during public comment. Additionally, SEC did not adequately substantiate that the primary benefit of the rule was a genuine problem or consider relevant factors in its evaluation of the costs of the rule.

[172] 42 U.S.C. § 263a; 42 C.F.R. pt. 493.

[173] CDC, Clinical Laboratory Improvement Advisory Committee (CLIAC) (last reviewed Nov. 9, 2023), https://www.cdc.gov/cliac/index.html.

requirements (e.g., with regard to practice of medicine and the requirement for a healthcare practitioner order for a laboratory test).

FDA is seeking to impose its regulatory regime on LDTs without any consideration for how FDA regulatory requirements, including QSR, would interact with or conflict with CLIA requirements. Redundant regulatory requirements hinder innovation, because they require regulated entities to establish different processes, procedures, and documentation to achieve the same goal of safe and effective products (e.g., the creation of a design history file to comply with the QSR). Implementation of different procedures requires additional personnel, systems, and time commitments (e.g., for training), all of which require additional resources. Recognizing the harmful effects on innovation of competing regulatory frameworks, Executive Order 13563 directs Executive Branch agencies to harmonize their regulatory requirements:

> Some sectors and industries face a significant number of regulatory requirements, some of which may be redundant, inconsistent, or overlapping. Greater coordination across agencies could reduce these requirements, thus reducing costs and simplifying and harmonizing rules. In developing regulatory actions and identifying appropriate approaches, each agency shall attempt to promote such coordination, simplification, and harmonization. Each agency shall also seek to identify, as appropriate, means to achieve regulatory goals that are designed to promote innovation.[174]

Contrary to the Executive Order, FDA's proposal makes no recognition of the need to harmonize with CLIA. Rather, FDA appears to view its mission as to override Congressional intent. Indeed, FDA refers to the FDA IVD regulatory requirements and CLIA laboratory requirements as a "bifurcated system" and states that "FDA views this bifurcated system of oversight as untenable and inconsistent with FDA's public health mission."[175] However, FDA fails to acknowledge that Congress created this bifurcated system through the passage of CLIA. It is not up to FDA, one of the two agencies in the bifurcated system, to end this system unilaterally via regulation. FDA's views on what constitutes better policy does not allow it to usurp the role of Congress.

As further discussed below, Congress considered changing the system multiple times over the past 15+ years—including through review of iterations of the VALID Act—but repeatedly failed to do so.[176] FDA rejects the notion that "additional oversight

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[174] Exec. Order No. 13,563, 76 Fed. Reg. 3,821 (Jan. 21, 2011).

[175] 88 Fed. Reg. 68,006, 68,010.

[176] Gail H. Javitt, FDA Regulation of LDTs, *in* Diagnostics at a Crossroads: Navigating IVD Regulation in a Changing Environment (Jeffrey Gibbs & Allyson Mullen eds., 2022).

of LDTs should be accomplished by granting new statutory authorities to CMS," stating that this would be a "problematic split in oversight, with the same types of tests being reviewed by different Agencies depending on where the test was made."[177] Divided jurisdiction can certainly cause difficult regulatory problems (e.g., with pepperoni frozen pizza regulated by USDA, and cheese frozen pizza regulated by FDA), but this is not a problem that FDA has the authority to fix. It is up to Congress to decide how the authority to regulate different categories of products is distributed between relevant agencies.

VI. FDA LACKS STATUTORY AUTHORITY TO REGULATE LDTS

As discussed above, the Proposed Rule is flawed in multiple respects. Even if it were not, the Agency lacks statutory authority to subject LDTs to the statutory requirements it seeks to apply.

A. The Proposed Rule Is Subject to The Major Questions Doctrine

For decades, the Supreme Court has recognized that even textually plausible agency interpretations of old legislation must give way to "'common sense'" when a federal agency invokes such laws to subject individuals or entities to significant federal requirements to which they have "never before been subject."[178] That is so because "[e]xtraordinary grants of regulatory authority are rarely accomplished through 'modest words,' 'vague terms,' or 'subtle devices,'"[179]and because the courts generally "presume that 'Congress intends to make major policy decisions itself, not leave those decisions to agencies.'"[180]

When agencies invoke longstanding legislation to justify significant new regulatory requirements, this "major questions doctrine" accordingly provides that "something more than a merely plausible textual basis for the agency action is necessary. The agency instead must point to 'clear congressional authorization' for the power it

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[177] 88 Fed. Reg. 68,006, 68,014.

[178] West Virginia v. EPA, 142 S. Ct. 2587, 2608 (2022) (quoting Brown & Williamson Tobacco Corp., 529 U.S. 120, 133 (2000) (rejecting FDA's attempt to regulate the safety of tobacco products) and citing Utility Air Regulatory Group v. EPA, 573 U.S. 302, 310, 324 (2014) (rejecting EPA's attempt to regulate greenhouse gas emissions from small sources despite its admitted textual plausibility)).

[179] *Id*. at 2609 (quoting Whitman v. Am. Trucking Ass'n, 531 U.S. 457, 468 (2001)).

[180] *Id*. (quoting United States Telecom Assn. v. FCC, 855 F. 3d 381, 419 (D.C. Cir. 2017) (Kavanaugh, J., dissenting from denial of rehearing *en banc*)).

claims."[181] At least three different categories of cases are subject to this clear statement rule:

- where Congress previously has considered but declined to expressly grant an agency the regulatory authority it claims;[182]
- where upholding the agency's claimed authority would subject a significant number of parties to new regulatory requirements;[183] and
- where compliance with the agency's new federal mandates would require "billions of dollars in spending each year."[184]

The Proposed Rule doesn't implicate merely one of these hallmarks for applying the major questions doctrine's clear statement rule; it triggers every single one of them.

First, as FDA well knows but never credibly acknowledges, Congress repeatedly has considered whether to subject LDTs to the Agency's regulatory authority and, if so, to what extent—often at FDA's urging and with the benefit of its technical assistance. Indeed, since 2006 alone, Congress has considered, but refused to pass, nearly a dozen different pieces of legislation[185] that would have empowered FDA to regulate LDTs either in whole or in part.[186]

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[181] *Id*. (quoting Utility Air, 573 U.S. at 324); *see also* Alabama Ass'n of Realtors v. HHS, 141 S. Ct. 2485, 2489 (2021) ("We expect Congress to speak clearly when authorizing an agency to exercise powers of vast economic and political significance.") (internal quotation marks omitted).

[182] *See, e.g.*, West Virginia, 142 S. Ct. at 2614 (citing Brown & Williamson, 529 U.S. at 159-160; Ala. Ass'n of Realtors, 141 S. Ct. at 2486-87; FTC v. Bunte Bros., 312 U.S. 349, 352 (1941) (holding that the FTC lacked jurisdiction over intrastate commercial transactions in part because of "the Commission's unsuccessful attempt in 1935 to secure from Congress an express grant of authority over [such] transactions").

[183] *See, e.g.*, Utility Air, 573 U.S. at 321-22; National Fed'n of Indep. Business v. OSHA, 142 S. Ct. 661, 665 (2022); *see also* MCI Telecomms. Corp. v. AT&T Co., 512 U.S. 218, 231 (1994) (rejecting a proposed regulation that would de-tariff "40% of a major sector of the [telecommunications] industry").

[184] King v. Burwell, 576 U.S. 473, 485 (2015); *see also* West Virginia, 142 S. Ct. at 2621; Utility Air, 573 U.S. at 324; Ala. Ass'n of Realtors, 141 S. Ct. at 2489; Brown & Williamson, 529 U.S. at 160; MCI, 512 U.S. at 231.

[185] *See, e.g.*, Genomics and Personalized Medicine Act of 2006, S. 3822, 109th Cong. (2006); Laboratory Test Improvement Act of 2007, S. 736, 110th Cong. (2007); Genomics and Personalized Medicine Act of 2007, S. 976, 110th Cong. (2007); Genomics and Personalized Medicine Act of 2008, H.R. 6498, 110th Cong. (2008); Modernizing Laboratory Test Standards for Patients Act of 2011, H.R. 3207, 112th Cong. (2011); Verifying Accurate, Leading-edge IVCT Development of 2020, H.R. 6102, 116th Cong. (2020); Verified Innovative Testing in American Laboratories Act of 2020, S.

While these bills differed from each other in significant ways, they have one thing in common: Not one of these proposals presumed that the 1976 Medical Device Amendments (MDA) to the FD&C Act already vested FDA with plenary authority to regulate LDTs like common medical devices. Yet rather than accept its decades-long failure to secure the very regulatory authority FDA now seeks to arrogate, the Proposed Rule takes the remarkable position that FDA in fact has had such authority ever since the MDA's passage in 1976—and simply elected for the past half century to ignore the statute's mandatory requirements for medical devices by "not enforc[ing] applicable requirements" and thereby allowing literally hundreds of thousands of what it now says are illegal LDTs to proliferate.[187]

That assertion beggars belief, and against a backdrop where Congress has spent the last two decades debating FDA's role in regulating LDTs, the Agency's attempt to source its regulatory authority in a 50-year-old statute that FDA refused to apply for decades makes this case indistinguishable from the many others in which federal agencies—including FDA itself—have sought to overcome Congress's refusal to authorize their actions by claiming that this legislation conferred such authority all along.[188]

3512, 116th Cong. (2020); Verifying Accurate, Leading-edge IVCT Development of 2021, H.R. 4128, 117th Cong. (2021); Verified Innovative Testing in American Laboratories Act of 2021, S. 1666, 117th Cong. (2021); Food and Drug Administration Safety and Landmark Advancements Act of 2022, S. 4348 § 821, 117th Cong. (2022).

[186] In addition to these introduced-but-rejected bills, FDA provided what it called "technical assistance" in connection with a discussion draft of the never-formally-introduced Diagnostic Accuracy and Innovation Act ("DAIA") in 2018. *See* DAIA Discussion Draft (released Mar. 17, 2017), https://bucshon.house.gov/sites/bucshon.house.gov/files/documents/daia%20discussion%20draft.pdf. In reality, FDA rewrote the legislation to grant itself the very regulatory authority its Proposed Rule now claims the Agency has had for over 50 years. *See* FDA, FDA's Views on the Diagnostic Accuracy and Innovation Act (DAIA) (Aug. 3, 2018), https://thefdalawblog.com/wp-content/uploads/2018/08/FDA-LDT-Draft-Leg.pdf.

[187] 88 Fed. Reg. 68,006, 68,008.

[188] *See, e.g.*, West Virginia, 142 S. Ct. at 2610 ("[W]e cannot ignore that the regulatory writ EPA newly uncovered conveniently enabled it to enact a program that, long after the dangers posed by greenhouse gas emissions 'had become well known, Congress considered and rejected' multiple times.") (quoting Brown & Williamson, 529 U.S. at 144; citing Ala. Ass'n, 141 S. Ct. at 2486 ("When the eviction moratorium expired in July, Congress did not renew it. Concluding that further action was needed, the CDC decided to do what Congress had not."); *id*. at 2621 (Gorsuch, J., concurring) ("[I]t [is] telling when Congress has considered and rejected bills authorizing something akin to the agency's proposed course of action. That too may be a sign that an agency is attempting to work around the legislative process to resolve for itself a question of great political significance.") (internal quotations, citations, and original alteration omitted); Bunte Brothers, 312 U.S. at 352 (invoking the FTC's "unsuccessful attempt … to secure from Congress an express grant of [the challenged] authority").

Second, FDA concedes that implementing the Proposed Rule would subject thousands of laboratories, hospitals, and healthcare providers to burdensome new federal regulations with which they never previously have been required to comply. The Proposed Rule acknowledges as much: It observes that "[d]iagnostic testing is a cornerstone of modern medicine; CDC estimates that 70 percent of medical decisions are based on laboratory test results" and further concedes that LDTs are both "ubiquitous" and "a growing sector of that market."[189]

The PRIA in turn lays bare the extraordinary impact that subjecting LDTs to FDA regulation will have on the practice of medicine in America. It estimates that, at a bare minimum, thousands of laboratories—and literally hundreds of thousands of distinct LDTs—would become subject to burdensome new federal requirements once the Proposed Rule takes full effect.[190] Indeed, it estimates that the Agency's proposal would impact 1.65 billion diagnostic tests that are performed every single year, even without accounting for the substantial increase in diagnostic testing prevalence that the Agency implicitly projects during the decades in which the Proposed Rule will be in effect.[191]

That makes this case just like *Utility Air*, where the Supreme Court rejected EPA's attempt to subject small sources to EPA's Prevention of Significant Deterioration (PSD) permitting regulations because doing so would cause "annual permit applications [to] jump from about 800 to nearly 82,000; annual administrative costs [to] swell from $12 million to over $1.5 billion; and decade-long delays in issuing permits [to] become common, causing construction projects to grind to a halt nationwide." [192,193]

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[189] 88 Fed. Reg. 68,006, 68,010.

[190] PRIA at 25.

[191] *Id.* at 28; *see also, e.g.*, *id*. at 24, anticipating that up to 15,552 new LDTs will be introduced—and presumably be used in myriad diagnostic procedures—each year.

[192] Utility Air, 573 U.S. at 322 (citing 75 Fed. Reg. 31514, 31557 (2010)); *see also* PRIA at 75-76, 85 (estimating that the Proposed Rule would subject as many as 160,800 existing LDTs and up to 15,552 new LDTs per year to the Agency's PMA, 510(k) premarket notification, or *de novo* application requirements at a combined cost of up to $113.4 billion in upfront regulatory compliance expenses and $12.26 billion in annually recurring compliance expenses for every year the rule is in effect).

[193] We recognize that these figures are drawn from the high-end estimates presented in the LDT PRIA and acknowledge that FDA believes the eventual numbers may be lower. But for purposes of evaluating whether "the breadth of the authority that the agency has asserted, and the economic and political significance of that assertion, provide a reason to hesitate before concluding that Congress meant to confer such authority," West Virginia, 142 S. Ct. at 2608—and especially in light of the Agency's admission that "it is difficult to estimate" both "the exact baseline number of manufacturers of IVDs offered as LDTs that would be affected by this rule" and "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," PRIA at 20-21—the Agency's admission (that its Proposed Rule may well affect so many products) supplies the appropriate analytical input.

Given the Agency's conceded inability to review and take timely action on both EUAs and traditional IVD applications when approximately 8000 COVID-related EUAs were submitted during the 29-month period between January 2020 and May 31, 2022,[194] it is hard to fathom how FDA thinks it could discharge its responsibilities once it is deluged with the tens of thousands of new LDT marketing applications its Proposed Rule would require between 3 ½ and 4 years after the Proposed Rule takes effect, and the thousands of additional applications it will face each year thereafter. As in *Utility Air*, "decade-long delays [will] become common" and innovation will be hampered as busineses await FDA action on their pre-submissions and applications (whether for traditional medical devices, IVDs, or LDTs).[195]

Combined with the Proposed Rule's other burdensome regulatory obligations—including new reporting requirements, establishment registration, device listing, product labeling, investigational use regulations, QSR, and other regulations FDA failed to enumerate, e.g., 21 C.F.R. Part 11, to which these hundreds of thousands of LDTs will become subject under the Proposal Rule—the demonstrable costs and regulatory burdens of complying with these new federal mandates leave no doubt that the Proposed Rule meets the third hallmark of a major question: the fact that it will impose billions of dollars in compliance costs on newly regulated parties.[196]

The Proposed Rule never grapples with these issues; it does not even acknowledge the major questions doctrine, let alone seek to justify its assertion of power within the controlling legal framework that doctrine supplies. At most, the Agency implicitly seeks to mute the doctrine's obvious applicability by repeatedly asserting that its views about the regulatory status of LDTs are "longstanding."[197]

But FDA's current position isn't "longstanding" in any sense that matters for purposes of the major questions doctrine. Despite the Agency's effort to source its asserted authority in the 1976 MDA, the Proposed Rule ultimately acknowledges that

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[194] *See* Jeff Shuren & William Maisel, FDA's Center for Devices and Radiological Health's Continued Efforts to Return to Normal: Reopening for All Pre-Submissions, FDA Voices (May 31, 2022), https://www.fda.gov/news-events/fda-voices/fdas-center-devices-and-radiological-healths-continued-efforts-return-normal-reopening-all-pre.

[195] Utility Air*,* 573 U.S. at 322.

[196] *See, e.g.*, West Virginia, 142 S. Ct. at 2621 ("[A]n agency must point to clear congressional authorization when it seeks to regulate a significant portion of the American economy or require billions of dollars in spending by private persons or entities.") (internal citations and quotations omitted).

[197] 88 Fed. Reg. 68,006, 68,015; *see also id*. at 68,017 (claiming that the Proposed Rule merely "would reflect FDA's longstanding view that LDTs are devices under the FD&C Act and would reflect the fact that the device definition in the FD&C Act does not differentiate between entities manufacturing the device").

FDA did not publicly announce this interpretation of the statute in a rulemaking document until 1997—more than two decades after the MDA's enactment.[198] This belated assertion of regulatory authority is far too thin a reed on which to rest significant, costly new regulatory mandates.

Indeed, it is far too thin a reed to support the Proposed Rule even on its own terms. Unfortunately for FDA, the PRIA's narrative[199] that LDT enforcement discretion was adopted in 1976, based on the specific characteristics of the LDTs then in use, is not corroborated by the 1997 ASR Rulemaking. Rather, the 1997 preamble invoked by FDA consists of only a single declarative sentence that FDA made while responding to a comment on a proposed rule that addressed an entirely different subject (analyte specific reagents, or ASRs). The preamble asserted FDA's belief that "clinical laboratories that develop [home brew] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act," without any supporting analysis—not even a citation to the MDA, let alone an attempt to situate its claim within the FD&C Act's overall statutory and regulatory framework.[200]

Furthermore, according to the 1997 preamble, FDA declined to regulate in-house developed tests in recognition that such tests have "contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health."[201] This rationale is far different from the one asserted in the PRIA, where FDA never mentions the harm that would come from loss of LDTs. Additionally, FDA's recognition in 1997 of the public health benefits of LDTs and the negative effects on public health of regulating them as devices undercuts the Proposed Rule's failure to ascribe any benefits to LDTs, a contradiction FDA makes no attempt to reconcile. In the intervening years, LDTs have "contributed to enhanced standards of medical care" in even more clinical settings than in 1997. FDA also acknowledges the "conjectural nature of the risk reduction."[202] Notwithstanding this

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[198] *See id.* (citing 62 Fed. Reg. 62,243, 62,249 (the "ASR Rulemaking," Nov. 21, 1997)); *but cf.* West Virginia, 142 S. Ct. at 2623 (Gorsuch, J., concurring) (noting that only "a 'contemporaneous' and long-held Executive Branch interpretation of a statute is entitled to some weight as evidence of the statute's original charge to an agency" (quoting United States v. Philbrick, 120 U. S. 52, 59 (1887)); *see also id*. at 2610 (majority opinion; quoting Bunte Bros., 312 U.S. at 352, for the proposition that "the want of assertion of power by those who presumably would be alert to exercise it, is equally significant in determining whether such power was actually conferred").

[199] *See* PRIA at 8, 18.

[200] *See* Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 62 Fed. Reg. 62,243, 62,249 (Nov. 21, 1997).

[201] *Id*.

[202] PRIA at 30.

concession, FDA treats these risk reduction benefits as well-established when calculating the benefits of the rule.

In describing the history of LDT regulation, FDA refers to factors that led it to exercise enforcement discretion, such as the use of manual techniques and local patients, FDA suggests that there was a contemporaneous policy decision that resulted in taking this approach. Yet this appears to be an ex post facto narrative. We are unaware of FDA even mentioning the possibility of having jurisdiction over LDTs until sixteen years after the MDA was enacted. And when the ASR rule was adopted, FDA did not mention any of the factors it now cites. Thus, history belies FDA's claim that it has had a long-standing policy of enforcement discretion for LDTs, and that the considerations that led to that policy no longer apply.

The 1997 preamble similarly undermines FDA's current interpretation of commercial distribution. After the brief aside regarding enforcement discretion, FDA concluded that LDTs were outside the scope of the rulemaking because the "focus of this rule is the classification and regulation of ASR's that move in commerce, not tests developed in-house by clinical laboratories or ASR's created in-house and used exclusively by that laboratory for testing services."[203] If anything, then, the 1997 rulemaking dicta FDA now invokes, as supposedly authoritative support for its current policy position, is fundamentally at odds with the Proposed Rule given its express acknowledgement that LDTs remain "in-house" and do not "move in commerce" like traditional medical devices subject to regulation under the MDA. [204]

At bottom, then, the Proposed Rule plainly raises a major question that is subject to the Supreme Court's repeated admonition that FDA "must point to 'clear congressional authorization' for the power it claims."[205]

For the reasons stated above, the Proposed Rule represents on a flawed set of assumptions, ignores contrary data, and relies upon an economic analysis that violates the APA. FDA's assertions to the contrary, regulating all LDTs as devices under the FD&C Act is bad policy. Yet, even if FDA's proposed transformation of diagnostic testing in the US were good policy, it would still be unlawful. As the Fifth Circuit recently stated in striking down another regulation, "The agency rule at issue here flouts clear statutory text and exceeds the legislatively-imposed limits on agency authority in the name of

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[203] *Id.* (emphasis added).

[204] *Id.*; *see infra* Section VI(C), (addressing the MDA's commercial distribution requirements). Even if it were timely (it isn't) and did not affirmatively undercut the Proposed Rule's legitimacy (it does), we note that the Agency's assertion "was controversial at the time and was never addressed by a court." West Virginia, 142 S. Ct. at 2610.

[205] West Virginia, 124 S. Ct. at 2609 (quoting Utility Air, 573 U.S. at 324).

public policy."[206] Although neither the Proposed Rule nor the PRIA mention it, the violation of these new requirements by a laboratory would be subject to criminal penalties.[207]

B. The FD&C Act Does Not Clearly Authorize FDA To Regulate LDTs as Medical Devices

The MDA does not supply the clear statement required to justify FDA's sweeping assertion of authority over LDTs. To the contrary, its text and structure affirmatively undermine the Proposed Rule's core claims.

1. The MDA Expressly Exempts Licensed Healthcare Professionals Who Manufacture Devices For Use In Their Medical Practice

FDA's central contention is that its authority to regulate LDTs as common medical devices stems from the MDA's definition of "device" in 21 U.S.C. 321(h)(1), which allegedly "encompasses test systems regardless of where or by whom they are manufactured. In particular, the definition contains no exception or limitation for devices manufactured by laboratories."[208]

But definitional plausibility on its own cannot supply the requisite clear statement for an agency's assertion of far-reaching regulatory authority; the Supreme Court repeatedly has rejected such an approach to gauging the scope and extent of an agency's power.[209] In the Fourth Circuit's words, these cases leave no doubt that "an expansive, vaguely worded definition is not akin to clear congressional authorization. So, in a

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[206] VanDerStok v. Garland, No. 23-10718, 2023 U.S. App. LEXIS 29956 at *4 (5th Cir. Nov. 9, 2023).

[207] 21 U.S.C. § 333.

[208] 88 Fed. Reg. 68,006, 68,018; *see also* 21 U.S.C. § 321(h)(1) (claiming that "[t]he inclusion of articles in the FD&C Act's definition of a device without regard to the identity of their manufacturer makes particular sense in the context of test systems. Today, in FDA's experience, there is little distinction between the test systems manufactured by laboratories and other manufacturers.").

[209] *See, e.g.*, Utility Air, 573 U.S. at 315-16, 319-21 (rejecting claims that Congress clearly authorized EPA to regulate greenhouse gases simply because they fell within a literal interpretation of statutory definition of "air pollutant"); Solid Waste Agency v. U.S. Army Corps of Engineers, 531 U.S. 159, 172-73 (2001) (rejecting claims that Congress granted the Army Corps of Engineers regulatory authority over isolated wetlands simply because they fall within the literal definition of "waters of the United States"); Brown & Williamson, 529 U.S. 120 (rejecting claims that Congress empowered FDA to regulate tobacco products even though those products fell within the FD&C Act's broad definitions of "drug," "device," and/or "combination product"); Train v. Colorado Public Interest Research Group Inc., 426 U.S. 1, 23-25 (1976) (rejecting claims that Congress authorized EPA to regulate nuclear materials otherwise regulated under the Atomic Energy Act even though they are plainly "radioactive materials" within the Clean Water Act's definition).

major-questions case, more is required before holding that the agency has been granted the asserted power."[210]

There is good reason for that approach. Statutory definitions almost never are operative on their own. Instead, they serve merely to supply meaning for individual terms of art that appear in a given statute's substantive provisions—that is, the provisions of a statute that actually establish **who** can or can't do **what**, **when** they can or can't do it, and **how** they can or can't act with respect to the terms defined elsewhere. That is the case here. The FD&C Act definitions set forth in 21 U.S.C. § 321 establish no freestanding legal rights, obligations, responsibilities, prohibitions, jurisdiction, or authority on their own; they are just dictionary entries "[f]or the purposes of this chapter" of the U.S. Code, and therefore lack any legal relevance outside of Title 21's operative provisions, which do establish **certain** substantive requirements with respect to **certain** devices if they are made or marketed by **certain** people in **certain** circumstances.

And those statutory provisions, as the Proposed Rule concedes, in fact do precisely what the Proposed Rule starts by denying: They expressly distinguish between devices that are manufactured by, on the one hand, medical device companies who design, market, and distribute their products to third parties in ordinary interstate commerce and, on the other hand, healthcare providers that manufacture and use such products in the course of treating patients.[211] Indeed, despite the Proposed Rule's claim that the statute's requirements apply to "test systems regardless of where or by whom they are manufactured,"[212] 21 U.S.C. § 360(g) draws no fewer than five different class-wide distinctions that expressly depend on the identity of a given product's manufacturer.[213]

This is a significant problem for the Proposed Rule. Given that the statute plainly states healthcare providers, which includes laboratorians, are exempt from the MDA's most basic registration, recordkeeping, reporting, inspection, and listing requirements for the devices they make and use in the course of treating patients,[214] then those devices assuredly cannot be subject to the Proposed Rule's far more burdensome and costly

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[210] N.C. Coastal Fisheries Reform Grp. v. Capt. Gaston LLC, 76 F.3d 291, 302 (4th Cir. 2023).

[211] *See* 21 U.S.C. § 360(g)(2) ("The foregoing subsections of this section shall not apply to … practitioners licensed by law to prescribe or administer drugs or devices and who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in the course of their professional practice.").

[212] 88 Fed. Reg. 68,006, 68,018.

[213] *See* 21 U.S.C. § 360(g)(1)-(5) (creating exceptions for pharmacies, licensed healthcare providers, persons engaged in research, teaching, or chemical analysis, wholesale distributors, and other classes of persons exempted by regulation); *see also* 21 U.S.C. § 360i(c)(1) (establishing comparable identity-based exemptions from the MDA's recordkeeping and reporting requirements).

[214] *See id.*

provisions: the 510(k) premarket notification, premarket approval, de novo classification requirements, and the QSR.[215] After all, it defies both law and logic to think that a given device must be subject to premarket notice, classification, or approval before it can be used even though its manufacturer need not be registered, maintain records, file reports, list its products, or be subject to inspection by the Agency.

Section 510(k) says so expressly. By its plain terms, that section applies *only* to a "person who is required to register under this section."[216] And the scope of both the statute's premarket approval and de novo classification provisions in turn are defined by cross-reference either directly to section 510(k), the aforementioned reporting, recordkeeping, and inspection requirements, or both.[217] Without belaboring the point, these repeated cross-references would make little sense if Congress intended these statutory provisions to apply to persons who expressly are exempted from those requirements.

Seeking a way out, FDA tries to minimize the MDA's explicit exemption for healthcare providers by claiming in a footnote that "these exemptions apply to practitioners, not entities such as corporate or hospital laboratories that employ licensed practitioners."[218] That assertion does not survive scrutiny. Taken seriously, this view of the law would impose liability (including potential felony liability) on a solo practitioner's personal service corporation even though Congress expressly immunizes the practitioner herself from the MDA's requirements. There is no principled basis—let alone one grounded in the statute's text, structure, or history—for distinguishing between large and small corporations for purposes of the statutory exemption.

In any event, FDA's footnote conflicts with baseline common-law principles.[219] Hospital and laboratories working with LDTs (whether they are incorporated or

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[215] *See, e.g.*, United Sav. Assn. of Tex. v. Timbers of Inwood Forest Associates, Ltd., 484 U.S. 365, 371 (1988) ("A provision that may seem ambiguous in isolation is often clarified by the remainder of the statutory scheme … because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law."); *see also* Utility Air, 573 U.S. at 321 ("[R]easonable statutory interpretation must account for both the specific context in which language is used and the broader context of the statute as a whole.") (internal citations and quotations omitted); Davis v. Mich. Dep't of Treasury, 489 U.S. 803, 809 (1989) ("[T]he words of a statute must be read in their context and with a view to their place in the overall statutory scheme.").

[216] 21 U.S.C. § 360(k).

[217] *See, e.g.*, 21 U.S.C. §§ 360c(f)(2)(A)(i)-(ii), (f)(4), (f)(6)(C), (i)(E)(i), (iii); 21 U.S.C.§ 360e(e)(1)(D).

[218] 88 Fed. Reg. 68,006, 68,018.

[219] *See, e.g.*, Astoria Fed. Sav. & Loan Ass'n v. Solimino, 501 U.S. 104, 108 (1991) ("Congress is understood to legislate against a background of common-law … principles."); United States v. Texas, 507 U.S. 529, 534 (1993) ("In order to abrogate a common-law principle, the statute must 'speak directly' to the question addressed by the common law.").

unincorporated, for-profit or not) act only through their employees, which is why—in accordance with familiar principles of agency and vicarious liability—the actions of a hospital or laboratory's employees acting within the scope of their employment are imputable to the entity. But those principles are not, and never have been, a one-way: Vicarious immunity principles are equally well-recognized in the law, since imposing liability on an employer when its employees engage in protected conduct almost invariably will stifle the employee's ability to engage in the protected conduct.

Finally, we note that hospital and corporate laboratories that develop, use, and communicate results from LDTs almost invariably are directed, supervised, and staffed by appropriately licensed healthcare providers; that is a basic requirement of CLIA.[220]

C. LDT's Are Not Introduced into Interstate Commerce for Commercial Distribution

The Proposed Rule is not merely inconsistent with the MDA's class-wide exemption for devices that healthcare professionals make and use in the course of their professional practice; it directly conflicts with the statute's interstate "commercial distribution" requirements. Far from subjecting any and all medical devices to the statute's 510(k) premarket notification, premarket approval, or de novo classification requirements, the statute instead limits those requirements to devices that are or will be "introduc[ed] or deliver[ed] into interstate commerce **for commercial distribution**."[221]

The distribution of a device in interstate commerce is similarly a threshold requirement for the applicability of many of the key regulatory requirements applicable to device manufacturers, including the requirements for medical device reporting, correction and removal, and registration and listing. For example, FDA's correction and removal requirements, 21 C.F.R. Part 806, define a manufacturer to include any person who:

> (1) Repackages or otherwise changes the container, wrapper, or labeling of a device in furtherance of the distribution of the device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user or consumer;

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[220] *See, e.g.*, 42 C.F.R. §§ 493.1357, 1363, 1405, 1411, 1417, 1423, 1443, 1449, 1455, 1461.

[221] *See* 21 U.S.C. § 360(k) (emphasis added); *see also id.* § 360c(c)(2)(C)(ii) (classification status dependent on whether a given device was "introduced or delivered for introduction into interstate commerce *for commercial distribution* before May 28, 1976, or is within a type of device which was *so introduced or delivered* before such date") (emphases added; internal enumeration omitted); *id.* § 360c(f)(1) (virtually identical); *id.* § 360e(b)(1) (virtually identical); *id.* § 360e(i)(1) (virtually identical).

> (2) Initiates specifications for devices that are manufactured by a second party for subsequent distribution by the person initiating the specifications; or
>
> (3) Manufactures components or accessories which are devices that are ready to be used and are intended to be commercially distributed and are intended to be used as is, or are processed by a licensed practitioner or other qualified person to meet the needs of a particular patient.[222]

LDTs originate in and remain at all times within the confines of the clinical laboratory. Clinical laboratories therefore cannot be considered manufacturers within the scope of the FD&C Act or key regulatory requirements.

The statute does not define "commercial distribution," so courts—and, therefore, agencies which hope to have their interpretations to withstand judicial scrutiny—must "look to the [phrase's] ordinary definition."[223] That meaning is not hard to find: "Commerce" refers to "the exchange or buying and selling of commodities especially on a large scale and involving transportation from place to place."[224] And in its most common and contextually appropriate sense, "distribution" refers to the "delivery" or "conveyance" of a good "from a main source" to another.[225] These mutually reinforcing definitions accordingly make clear than the statute's premarket submission requirements apply only where a given device is the subject of an exchange from one person or entity to another, and from one place to another.

That understanding makes perfect sense in the context of typical medical devices. For example, when a traditional device manufacturer seeks to produce a product for sale to hospitals, the commodity good it is proposing to introduce will be transferred from the sponsor to third parties, from one place to another, as part of an ordinary business transaction (i.e., the exchange of goods for cash). LDTs, by contrast, bear no resemblance to this archetype. Rather than being produced for commercial sale and external distribution to third parties, LDTs are designed within a laboratory, for use by the laboratory; are not made commercially available for sale outside the laboratory to unaffiliated third parties; and do not leave the lab's control (or that of its affiliates, which FDA's own regulations expressly exempt from the MDA's requirements[226]). There is no

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[222] 21 C.F.R. § 806.2(h); *see also* 21 C.F.R. §§ 803.3, 807.65.

[223] CSX Transp., Inc. v. Ala. Dep't of Revenue, 562 U.S. 277, 284 (2011).

[224] Philip Babcock Gove and the Merriam-Webster editorial staff, Webster's Third New International Dictionary of the English Language, Unabridged, Merriam-Webster (2002) [hereinafter Webster's Dictionary].

[225] *Id*.

[226] *See* 21 C.F.R. § 807.3(b); *see also* 41 Fed. Reg. 37,458 (1976) ("The definition of the term "commercial distribution" in proposed § 807.3[b] specifically excludes internal transfers of a device

transfer of title with an LDT. Neither the clinician nor the patient receive the test; they receive information from a service performed by the laboratory, using the LDT as a tool to perform that service. The Agency does not have to take our word for it: This is precisely the distinction FDA itself drew in the ASR Rulemaking.[227]

The Proposed Rule does not credibly attempt address these obvious points, including its own prior recognition of this critical distinction. The entirety of its current analysis appears in a single column of the Federal Register declaring that "'commercial distribution' does not require the physical transfer of an object, as some commentators have argued. Instead, the legislative history, FDA's near-contemporaneous regulation, and at least one judicial decision reflect that the phrase 'commercial distribution' means 'on the market.'"[228] That claim is not persuasive—much less sufficient to demonstrate the existence of a clear statement demonstrating that the MDA's premarket notification, classification, or approval provisions apply to LDTs.

To start with, FDA's invocation of a single snippet of "the legislative history" is no substitute for a credible textual analysis of the statute's actual language and the ordinary meaning of the words Congress actually used.[229] In 2023, to use the federal government's own words, FDA's legislative-history-only "approach is a relic from a 'bygone era of statutory construction'" that no serious court would credit if and when it is challenged.[230]

But even if the Proposed Rule's legislative-history-only approach were a legitimate form of statutory interpretation, it is hard to see how the quoted excerpt helps the Agency. Saying that "commercial distribution" means "on the market" just begs the question of what exactly "on the market" means. Dictionary definitions are no help to FDA: The "market" is "a sphere within which price-making forces operate and in which exchanges in title tend to be followed by actual movement of goods," and placing a product "on the market" typically means to put an item "up for sale" or to make it

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occurring within an organization.")

[227] 62 Fed. Reg. 62,243, 62,249 (expressly distinguishing "ASR's that move in commerce" from "tests developed in-house by clinical laboratories or ASR's created in-house and used exclusively by that laboratory for testing services").

[228] 88 Fed. Reg.68,006, 68,021.

[229] *See, e.g.*, Food Mktg. Inst. v. Argus Leader Media, 139 S. Ct. 2356, 2364 (2019) ("In statutory interpretation disputes, a court's proper starting point lies in a careful examination of the ordinary meaning and structure of the law itself. Where, as here, that examination yields a clear answer, judges must stop. Even those of us who sometimes consult legislative history will never allow it to be used to 'muddy' the meaning of 'clear statutory language.'") (quoting Milner v. Dep't of the Navy, 562 U.S. 562, 572 (2011)); *see also* Ratzlaf v. United States, 510 U.S. 135, 147-148 (1994) ("[W]e do not resort to legislative history to cloud a statutory text that is clear.").

[230] Webster's Dictionary.

"available for purchase" within that sphere.[231] But again, title to an LDT is never transferred from the laboratory to anyone else, and there is no actual movement of the LDT. In contrast to traditional medical devices, LDTs remain within the laboratory, for use by the lab, at the request of a licensed healthcare provider, and, in accordance with CLIA, under supervision and direction of a licensed professional. Ultimately, then, FDA's attempt to replace the statute's actual words with different ones it found in the legislative history only undermines its claim.

The Agency's attempted recharacterization of its regulatory definition fares no better. Though the Proposed Rule claims the regulation's preamble similarly "equated" the phrase "commercial distribution … with the phrase 'on the market,'" 88 Fed. Reg. at 68,021, the regulation's actual text still implements that concept by expressly requiring "distribution" of the product, not merely that it exist.[232] As set forth above, that word requires a "delivery" or "conveyance" of a good "from a main source," and indeed, the Final Rule's preamble took pains to emphasize that this requirement is satisfied only where the product at issue is transferred to an unaffiliated third party—not just that the product exists. [233] That is why the actual regulation specifically exempts the "[i]nternal or interplant transfer of a device between establishments within the same parent, subsidiary, and/or affiliate company" without regard to whether one of those entities has sold the product to the other. [234] And again, that is why the ASR Rulemaking expressly distinguished between "ASR's that move in commerce" and "tests developed in-house by clinical laboratories or ASR's created in-house and used exclusively by that laboratory for testing services."[235]

That leaves only FDA's invocation of a single district court decision issued by the Western District of Michigan in 1985,[236]—a precedent that has been cited all of three times in the nearly 40 years it has been on the books, and never once for the proposition FDA now says it stands for. Yet even that case fails to support FDA's apparent view that no transfer, movement, transportation, or exchange of title between unaffiliated parties is required to trigger these provisions of the statute, let alone that the MDA applies to LDTs that never leave the laboratory in which they are produced and consumed.

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[231] *Id.*

[232] *See* 21 C.F.R. § 807.3(b) ("Commercial distribution means any *distribution of a device* intended for human use which is held or offered for sale.") (emphasis added).

[233] Webster's Dictionary; *see* 42 Fed. Reg. 42,520, 42,520 ("The Commissioner agrees that premarket notification is not required when a device is to be shipped from a foreign subsidiary to a domestic parent establishment *and there is no distribution outside the company*.") (emphasis added).

[234] 21 C.F.R. § 807.3(b)(1).

[235] 62 Fed. Reg. 62,243, 62,249.

[236] *See* 88 Fed. Reg. 68,006, 68,021 (invoking United States v. An Article of Device Consisting of 1,217 Cardboard Boxes, 607 F. Supp. 990, 994–95 (W.D. Mich. 1985)).

Instead, that case arose from a traditional device manufacturer's introduction without premarket notification of a prosthetic ligament device; the parties' only dispute turned on whether the defendant's product was the same or different from a pre-1976 version of the product that admittedly lacked the targeted product's innovative "'H-Beam' longitudinal sewing" that "ma[d]e the vascular graft less elastic and smaller in diameter" than the predecessor version cited by the defendant.[237] Given the carefully circumscribed contours of the parties' dispute, the government itself "argue[d] that the FDA's definition of 'commercial distribution' has only minor relevance to this action . . . since the device in question did not exist prior to enactment of the [MDA]," and the district court fully agreed.[238] Suffice it to say, that precedent hardly justifies the Agency's current interpretation of the statute, much less the new regulatory mandates that FDA's interpretation would impose for the first time since the MDA's passage nearly 50 years ago.

We recognize that FDA disagrees with our interpretation of the statute's text, structure, and history. But in this major questions case, where the Agency itself admits that billions of dollars and billions of tests and the treatment of hundreds of millions of Americans are at stake, the Agency's attempt to cobble together a statutory defense of its plan to revolutionize the regulation of diagnostic testing falls well short of clear statement needed to justify its actions.

VII. CONCLUSION

Laboratory Developed Tests play a critical role in health care in the United States today. In its Proposed Rule, FDA seeks to completely reshape this sector in its own image. For the reasons stated above, FDA lacks the legal authority to do this. That authority resides solely with Congress.

Moreover, FDA's proposal, if adopted, will almost surely backfire. In questing to regulate LDTs, FDA has selectively cited a hodgepodge of sources, incorrectly calculated risks of LDTs, dramatically overstated estimated benefits, understated some costs to laboratories and ignored many others, discounted another $1.7 billion in laboratory expenses by calling them "transfers", and never mentioned the benefits provided by LDTs. The proposal blithely accepts the inevitable shuttering of laboratories due to these

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[237] *Id*. at 995.

[238] *See id*. ("I find myself in agreement with the Government that the device which it has seized is not the same device manufactured by Meadox prior to enactment of the amendments."); *see also id*. at 997 ("The seized device did not exist before 1978, and necessarily does not meet the Compliance Polic[y] Guide criteria. Stryker [therefore] has failed to prove even one element of the 'commercial distribution' exemption.").

new costs, while speculating that the closing of laboratories will somehow spur innovation by IVD manufacturers. Furthermore, the huge increase in pre-submissions, marketing applications, and other demands on FDA will likely lead to FDA's inability to cope with diagnostic submissions, whether from laboratories or companies selling distributed products, to the detriment of everyone.

The Coalition agrees with FDA that diagnostic testing is crucial to healthcare. That is why we strongly oppose FDA's proposed regulation.

Respectfully submitted,

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