AMERICAN CLINICAL LABORATORY ASSOCIATION

December 4, 2023

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

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

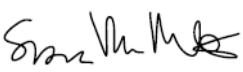
The American Clinical Laboratory Association (ACLA) submits the attached comments on FDA's Proposed Rule, "Medical Devices; Laboratory Developed Tests" (Docket No. FDA-2023-N-2177) ("Proposed Rule") which, if finalized, would subject laboratory developed tests (LDTs) to regulation as medical devices.

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

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

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

Sincerely,



Susan Van Meter
President

COMMENTS OF THE
AMERICAN CLINICAL LABORATORY ASSOCIATION

Contents

Executive Summary 1
Discussion 5
I. Device Regulation is Wrong for LDTs and Would Undermine Innovation and Access to Diagnostic Testing. 5
A. LDTs are professional services, not devices. 5
B. Applying device law would undermine innovation in diagnostics and access to critical testing services. 7
II. LDTs Are Subject to Robust Regulation and Review. 18
A. FDA's history of inconsistent positions on LDTs. 18
B. CLIA applies to all clinical laboratories and LDTs. 20
C. State laws impose additional requirements on laboratory testing services. 23
D. Payers scrutinize LDTs for coverage decisions. 24
III. FDA's Proposed Rule Fails to Recognize the Significant Contributions of LDTs to the Public Health. 25
A. LDTs drive advances in the public health by innovating at the pace of science. 25
B. LDTs are essential for meeting current clinical care needs. 31
IV. FDA's Characterization of LDTs is Inaccurate. 36
A. FDA's methodology for critiquing LDTs is flawed. 36
B. FDA's specific critiques are inaccurate. 38
V. FDA's Cost-Benefit Analysis is Flawed in Numerous Ways and Cannot Support Finalizing the Proposed Rule. 46
A. FDA underestimates the costs of the Proposed Rule. 46
B. The claimed benefits of the Proposed Rule are dramatically overstated. 54
VI. The Proposed Rule Raises Significant Legal Concerns. 59
A. LDTs are not "devices" under the FDCA. 59
B. Had Congress provided FDA with authority over LDTs, it would have done so expressly. 64
C. LDTs cannot be subject to any FDCA authorities that require devices to be introduced or delivered into interstate commerce for commercial distribution. 65
D. LDTs are not "held for sale" as required under FDCA Section 301(k). 67
E. Imposing device law on LDTs would violate the First Amendment. 68
F. FDA regulation would interfere with the practice of medicine. 70
G. The NPRM Fails to Comply with Section 553(b) of the Administrative Procedure Act. 70
VII. The Agency Could Revise the Rule to Reduce, but not Eliminate, the Net Negative Impact of the Rule to Public Health. 71
A. Grandfathering for existing tests. 71

B. Extended implementation timeline. 72
C. New York State and MolDX programs. 73
D. Flexible modifications policy. 74
E. Enforcement discretion for low-volume tests. 75
F. Classification panels. 75
G. CLIA regulation. 75
H. Request for information (RFI). 76
I. Equal treatment of LDT developers. 76
Conclusion 77

Exhibit 1: Chris Carrigan, Global Economics Group, Review of the Food and Drug Administration's Preliminary Regulatory Impact Analysis for its Medical Devices; Laboratory Developed Tests Proposed Rule

EXECUTIVE SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DISCUSSION[1]

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

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

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

A. LDTs are professional services, not devices.

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

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

Pre-analytical steps

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

---

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

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

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

Analytical steps

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

Post-analytical steps

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

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

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

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

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

1. Device regulation would slow innovation.

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

a) Device regulation would divert limited laboratory resources.

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

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

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

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

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

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

---

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

[4] *Id.* at 122.

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

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

[7] 21 CFR § 866.5950.

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

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

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

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

---

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

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

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

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

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

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

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

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

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

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

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

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

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

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

---

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

[12] *Id.*

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

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

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

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

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

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

---

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

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

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

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

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

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

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

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

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

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

---

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

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

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

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

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

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

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

---

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

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

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

[22] *Id.*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

---

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

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

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

[29] *Id.*

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

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

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

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

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

II. LDTs Are Subject to Robust Regulation and Review.

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

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

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

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

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

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

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

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

---

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

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

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

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

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

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

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

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

B. CLIA applies to all clinical laboratories and LDTs.

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

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

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

---

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

[37] 42 CFR § 493.1449.

[38] *Id.* § 493.1455.

[39] *Id.*

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

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

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

2. CLIA imposes strict quality requirements and proficiency standards.

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

---

[40] *Id.* § 493.1487.

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

[42] 42 CFR § 493.1457.

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

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

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

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

3. CLIA is supplemented by rigorous accreditation standards.

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

---

[45] *Id.*

[46] *Id.* §§ 493.1200 - 493.1299.

[47] 42 CFR §§ 493.801 - 493.807.

[48] *See id.* §§ 493.821 - 483.865.

[49] *Id.* § 493.801(a).

[50] *Id.* §§ 493.803(b), 493.1806.

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

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

[53] *See* 42 U.S.C. § 263a(d).

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

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

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

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

---

[54] *Id.* § 263a(e)(2)(A).

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

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

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

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

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

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

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

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

D. Payers scrutinize LDTs for coverage decisions.

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

---

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

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

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

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

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

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

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

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

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

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

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

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

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

---

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

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

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

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

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

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

---

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

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

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

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

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

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

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

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

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

---

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

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

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

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

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

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

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

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

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

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

2. LDTs are a critical public health tool.

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

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

---

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

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

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

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

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

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

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

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

---

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

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

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

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

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

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

3. LDTs advance therapeutic product development.

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

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

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

---

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

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

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

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

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

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

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

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

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

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

---

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

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

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

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

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

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

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

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

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

---

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

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

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

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

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

2. LDTs perform better than cleared or approved tests.

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

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

---

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

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

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

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

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

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

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

---

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

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

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

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

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

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

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

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

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

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

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

---

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

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

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

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

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

IV. FDA's Characterization of LDTs is Inaccurate.

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

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

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

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

Even if FDA were correct to be concerned about the identified LDTs (it is not), those LDTs would represent only a tiny fraction of a percent of LDTs being performed today, or ever. Based on our count in reviewing the Proposed Rule and the cited references, FDA appears to have identified approximately 160 LDTs that it implies are unreliable or otherwise problematic. However, even using FDA's estimate of 80,400 available LDTs, FDA's anecdotal references reflect only ~0.2% of available LDTs. Stated differently, FDA has offered no evidence of harm with respect to 99.8% of currently available LDTs. FDA also makes no attempt to contextualize its concerns in the decades of reliance on LDTs, during which time likely billions of LDTs have been performed to inform patient care. Instead, FDA acknowledges that it has not "systematically collect[ed] information" on LDTs,

---

[121] Indeed, at several points within the preamble to the Proposed Rule, FDA expressly acknowledges that its evidence is "anecdotal." *See* 88 Fed. Reg. at 68010 ("As the testing landscape as evolved, information about these tests in the scientific literature, news articles, and **anecdotal reports** submitted to the Agency, among other sources, has exposed evidence of problems associated with these tests.") and 86012 ("As noted above, collectively, this information, **though anecdotal**, points to **potential problems** among IVDs offered as LDTs….").

[122] Alyssa L. Halbisen & Christine Y. Lu, T*rends in Availability of Genetic Tests in the United States, 2012–2022*, 13 J. PERSONALIZED MED. 638 (2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10142561/.

proposes to apply its device authorities to such tests "[b]ased on current safety signals," and points to "limitations in the data" as justification for extrapolating evidence in its cost-benefit analysis.[123]

Second, many of FDA's sources of "evidence" are unverified, and it is inappropriate to base this sweeping regulatory action on unsubstantiated anecdotes and conjecture. For example, FDA states that it has "received multiple complaints, adverse events reports, and other allegations identifying problems with IVDs offered as LDTs," but then immediately admits in a footnote that "FDA has not confirmed the veracity of the allegations or facts in every complaint report, and allegation."[124] FDA likewise points to legal complaints filed by consumers, shareholders, litigants, and investors, but these complaints—by definition—are based on unproven facts. If LDTs actually performed poorly, treating physicians would stop using them and would call attention to the medical community regarding the bad test experience. But this is not the case: physicians continue to rely on LDTs every day to inform patient care.

Third, even if FDA's stated concerns with LDTs were verified, the Agency has not demonstrated that these concerns would be addressed by FDA regulation. This is a recurring issue with FDA assertions that it must regulate LDTs to protect the public health. Indeed, following FDA's 2015 memo citing 20 case studies of LDTs that it claimed constituted "public health evidence for FDA oversight of laboratory developed tests," an analysis authored by the Association for Molecular Pathology (AMP) demonstrated that the harms identified by FDA were largely fictional and few would actually be addressed by FDA regulation.[125] And FDA's current assertions that it must regulate LDTs to protect the public health are similarly unjustified because the Agency has offered no comparison to the prevalence of these concerns with cleared and approved IVDs. FDA has not demonstrated that LDTs present any greater risk than cleared and approved IVDs.

FDA raises concerns that LDTs sometimes yield inaccurate results, but cleared and approved IVDs also yield inaccurate results. Cleared and approved IVDs do not have perfect analytical or clinical validity. In fact, every test has a certain sensitivity and specificity, reflecting that false positives and false negatives are possible. Depending on a variety of factors, the sensitivity and specificity of tests may be relatively high, but in other cases, the sensitivity and specificity may be lower. For example, in 2022, a novel kidney test was classified through the De Novo pathway with sensitivity ranging from 76% to 93% and specificity ranging from 45% to 51%, and with precision/reproducibility studies generating high coefficients of variation across sites and lots (9.1% to 18.3%).[126] Notwithstanding that level of accuracy, FDA concluded that the value of having this tool available to clinicians outweighed the potential for false negative and false positive results. But applying the same reasoning that FDA applies to LDTs, the fact that this test has inaccurate results would render this test "problematic."

---

[123] 88 Fed. Reg. at 68008, 68010.

[124] *Id.* at 68011.

[125] AMP, *Facts FDA Ignored: An analysis of the FDA report, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies"* (Dec. 13, 2015), https://www.amp.org/AMP/assets/File/position-statements/2015/AMPResponseFDACaseReportFinal.pdf?pass=54.

[126] *See, e.g.*, Decision Summary for DEN130031 (NEPHROCHECK® Test system), https://www.accessdata.fda.gov/cdrh_docs/reviews/den130031.pdf (last visited Nov. 8, 2023).

FDA also receives reports and allegations regarding poor performance of cleared and approved IVDs. FDA's own Manufacturer and User Facility Device Experience (MAUDE) database includes many complaints associated with various approved or cleared IVDs. Furthermore, there have been many recalls of FDA-cleared or -approved diagnostics for quality or other issues that impact the accuracy of those tests. In short, FDA regulation is not a panacea, and the claims embedded in the Proposed Rule vastly overstate the claimed benefits of subjecting LDTs to the burdens of FDA regulation.

FDA's proposal to apply device authorities to LDTs on the basis of anecdotal and unproven evidence without comparison to available evidence for IVDs is hypocritical of an agency that demands much more from the entities it regulates. The Agency demands that device applications are supported by systematically collected "valid scientific evidence,"[127] and accepts real world evidence only when the underlying data meets this threshold.[128] The Agency should not be proposing sweeping policy changes on the basis of anything less. In fact, FDA's own regulation provides that "[i]solated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence,"[129] which is exactly the type of evidence that FDA is relying upon to justify this vast expansion of its regulatory reach.

B. FDA's specific critiques are inaccurate.

It is not possible, nor necessary, to respond to every allegation that FDA makes in its Proposed Rule in this compressed comment period.[130] Nonetheless, it is imperative to correct the record with regard to certain categories of tests that FDA has broadly characterized as problematic. In particular, ACLA was disappointed with how FDA mischaracterized the quality, validity, and importance of LDTs for COVID-19, NIPS, and oncology. FDA cannot finalize the Proposed Rule based on its mischaracterization of these tests.

---

[127] *See* 21 CFR § 860.7(c)(1)-(2) ("[T]he agency relies only on valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective.") & ("Valid scientific evidence is evidence from well-controlled clinical investigations, partially controlled studies, studies and objective trials with matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.").

[128] FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: USE OF REAL-WORLD EVIDENCE TO SUPPORT REGULATORY DECISION-MAKING FOR MEDICAL DEVICES (2017), https://www.fda.gov/media/99447/download.

[129] *See* 21 CFR § 860.7(c)(2).

[130] ACLA remains disappointed that the Agency rejected multiple requests to extend the comment period beyond 60 days, even while the Agency took at least seven months to develop its proposed rule. *See* Mark McCarty, *Hillebrenner Says FDA No Longer Waiting on Congress for LDT Regulation*, BIOWORLD.COM (Mar. 1, 2023), https://www.bioworld.com/articles/694701-hillebrenner-says-fda-no-longer-waiting-on-congress-for-ldt-regulation?v=preview (announcing FDA's intentions to proceed with rulemaking as early as March 1, 2023).

1. FDA's characterization of COVID-19 LDTs is inaccurate.

FDA's characterization of COVID-19 LDTs is both incomplete and inaccurate. FDA completely ignores that LDTs were critical to the American response to the PHE, and instead draws inaccurate conclusions that threaten to erode the public's trust in clinical laboratories. As an initial matter, the first confirmed case of COVID-19 in the United States was diagnosed by an LDT, even before the PHE was formally declared. And as the pandemic evolved, LDTs continued to be a source of reliable testing.

Specifically, once the PHE was declared, LDTs were among the *first* reliable testing options available to Americans because test kits were not available. Although FDA granted an EUA for the CDC SARS-CoV-2 molecular diagnostic test kit, the test kit could not be validated by other laboratories and was unusable for weeks.[131] By relying only on IVDs for COVID testing, American testing capacity lagged far behind that of other countries.[132] It was only after FDA issued a more flexible policy to allow laboratories developing LDTs to step in that testing capacity for Americans soared. Within two and a half months of issuing the policy, 245 laboratories had notified FDA that they would begin testing.[133]

FDA's characterization of COVID-19 LDTs in the preamble to the Proposed Rule is also based on anecdotal evidence that is improperly extrapolated without context. For example, FDA points to the first 125 COVID-19 LDT EUA submissions as proof that laboratories do not perform appropriate or adequate validation studies.[134] The Agency claims that 82 of these submissions "showed test

---

[131] The problems with the CDC test are well documented. *See, e.g.*, Shawn Boburg et al., *Inside the Coronavirus Testing Failure: Alarm and Dismay Among the Scientists Who Sought to Help*, WASH. POST (April 5, 2020); SUZANNE MURRIN, HHS OFFICE OF THE INSPECTOR GENERAL, FDA REPEATEDLY ADAPTED EMERGENCY USE AUTHORIZATION POLICIES TO ADDRESS THE NEED FOR COVID-19 TESTING (2022), https://oig.hhs.gov/oei/reports/OEI-01-20-00380.pdf ("CDC's first test was unusable for many weeks while no other test was authorized.").

[132] Shawn Boburg, et al., *supra* note 131 (Whereas the United States had performed a total of 2,009 tests by February 12, "[i]n South Korea, 1,000 people were being tested each day by mid-February, a number that would increase more than tenfold by the end of the month. The Geneva-based World Health Organization, meanwhile, had already delivered 250,000 diagnostic tests designed and manufactured by a German lab to 70 laboratories around the world."). *See also*, Barbara J. Evans and Ellen Wright Clayton, *supra* note 87.

[133] SUZANNE MURRIN, *supra* note 131. Indeed, FDA's evolving COVID-19 Testing Policy recognized the accuracy and reliability of LDTs compared to IVD test kits. At one point, FDA modified its testing policy to extend to LDTs and IVDs for COVID-19 serology tests, but then retracted this policy with regard to test kits after discovering that several of the commercially manufactured tests were unreliable. FDA, GUIDANCE FOR INDUSTRY: POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY 7 (2020) ("FDA has become aware that a concerning number of commercial serology tests are being promoted inappropriately, including for diagnostic use, or are performing poorly based on an independent evaluation by the NIH, indicating that greater FDA oversight of commercial serology tests is important to protect the public health.") (citations and footnotes omitted). While laboratories could still introduce serology tests without EUA authorization, kit manufacturers could not. The distinction FDA drew in its own policy was clear: without FDA oversight, commercial manufacturers did not produce reliable tests; but CLIA oversight of laboratories ensured the quality of LDTs.

[134] 88 Fed. Reg. 68011.

design or validation problems," but fails to acknowledge that many of these supposed problems were a direct result of incomplete and constantly changing guidance from FDA, as well as the realities of responding in real-time to a public health emergency where laboratories were doing all they could to expand the testing capacity of the country.

In particular, in FDA's memorandum detailing this assessment of the first 125 COVID-19 LDT EUA submissions, the Agency asserts that issues with validation included that "laboratories did not provide minimal descriptive information about their validation studies in the EUA request for FDA to assess the performance."[135] However, failure to provide this descriptive information does not affect—at all—the quality of the validation studies themselves. Rather, failure to provide this information reflects that laboratories, accustomed to validating tests pursuant to CLIA, CAP, New York State requirements, and other industry standards, did not have clear or consistent direction from FDA regarding which information to provide in an EUA request.

As another example from the memorandum, FDA asserts that "[t]he most common issue with analytical validation was related to use of synthetic DNA or small fragments of synthetic RNA," rather than viral RNA, but then immediately admits that "viral RNA was difficult to obtain through April 2020, and so FDA had recommended," but did not require, "that if synthetic RNA was used, validation should include full length or long strand RNA to closely approximate natural viral RNA."[136] FDA also acknowledged that "alternative approaches, such as creating contrived specimens with synthetic DNA, can be used, particularly in the early stages of an emergency when availability of viral RNA is limited."[137] It is wrong to portray clinical laboratories as being unable to perform appropriate or adequate validation studies when such studies were performed based on FDA guidance and the best available materials in the midst of a global pandemic.

It is also wrong to suggest that FDA's dissatisfaction with the quality of EUA submissions directly translated to bad tests, particularly when "[i]n the majority of cases, the FDA worked with the laboratories to correct the issues and permit continued testing."[138] Indeed, in a similar context—EUAs for MPOX diagnostics—a published report details how FDA's requests for additional validation studies or data did not meaningfully affect test performance and offered minimal benefits.[139] Laboratories report similar experiences with COVID-19 diagnostics.

Finally, it is wrong to suggest that the identified challenges with test design and validation were unique to laboratories. Rather, as FDA acknowledged, "[s]imilar problems were seen with commercial manufacturers" at the time.[140] And, contrary to the implication that LDTs perform worse than test kits, at least one study found 100% agreement between certain commercial and laboratory

---

[135] ELIZABETH HILLEBRENNER, ASSOCIATE DIRECTOR FOR SCIENTIFIC AND REGULATORY PROGRAMS, CDRH, FDA, MEMORANDUM: SUMMARY OF 2020 ASSESSMENT OF THE FIRST 125 EUA REQUESTS FROM LABORATORIES FOR MOLECULAR DIAGNOSTIC TESTS FOR SARS-COV-2 (Sept. 22, 2023).

[136] *Id.*

[137] *Id.*

[138] Jeffrey Shuren & Timothy Stenzel, *Covid-19 Molecular Diagnostic Testing—Lessons Learned*, 383:e97 N. ENG. J. MED. (2020), *https://doi.org/10.1056/nejmp2023830*.

[139] Caldera, *supra* note 10. .

[140] SHUREN AND STENZEL, *supra* note 138.

tests for SARS-CoV-2.[141] Moreover, throughout the public health emergency, there were reported accuracy and quality concerns with EUA-authorized test kits.[142]

Other evidence cited by FDA also cannot reasonably be construed to suggest that CLIA-certified, high-complexity clinical laboratories systematically produced bad COVID-19 tests. For example, FDA cites a *ProPublica* report on a COVID-19 test offered by a laboratory in Chicago that missed 96 percent of positive cases,[143] but that laboratory had so many CLIA deficiencies that a CMS report concluded the public was put in "immediate jeopardy" by the laboratory's operation.[144] Accordingly, the poor performance of this laboratory's COVID-19 LDT is not indicative of the performance of LDTs developed by high-complexity laboratories that are operating in compliance with CLIA.

2. FDA's characterization of non-invasive prenatal screening (NIPS) is inaccurate.

NIPS is widely viewed as a breakthrough in prenatal care, but FDA's characterization of these tests reflects a fundamental misunderstanding of their intended use and their role in prenatal care. First, FDA's preamble distorts the difference between screening and diagnostic testing – a basic tenet of laboratory medicine. NIPS analyzes cell-free DNA that is naturally shed by the placenta cells into the pregnant patient's blood. NIPS tests are screening tests: they are intended to assess whether a pregnant patient may be carrying a fetus at increased risk of having a genetic disorder. Accordingly, a "positive" NIPS result indicates that the fetus is at higher risk of having a genetic disorder, but it is not a diagnosis. To obtain a firm diagnosis, further diagnostic testing should be used. However, a "negative" diagnostic test result does not mean that the "positive" NIPS result was wrong or a "false

---

[141] Kerry Dust et al., *Comparison of Commercial Assays and Laboratory Developed Tests for Detection of SARS-CoV-2* (2020), 285 J. VIROLOGICAL METHODS 113970 (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7482591/ (comparing the performance of two commercial assays, the cobas® SARS-CoV-2 (Roche Diagnostics) and Xpert® Xpress SARS-CoV-2 (Cepheid®) tests, and a laboratory developed RT-PCR test adapted for use on the Hologic® Panther Fusion® (Hologic®) instrument as well as Bio-Rad and QIAGEN real-time PCR detection systems).

[142] *See, e.g.*, FDA, *Potential for False Positive Results with Certain Lots of Ellume COVID-19 Home Tests Due to a Manufacturing Issue: FDA Safety Communication* (Oct. 5, 2021) https://www.fda.gov/medical-devices/safety-communications/potential-false-positive-results-certain-lots-ellume-covid-19-home-tests-due-manufacturing-issue-fda#Actions (class I recall affecting around 2 million tests); FDA, *Do Not Use Certain SD Biosensor Pilot COVID-19 At-Home Tests: FDA Safety Communication* (May 4, 2023), https://www.fda.gov/medical-devices/safety-communications/do-not-use-certain-sd-biosensor-pilot-covid-19-home-tests-fda-safety-communication (class I recall affecting over 500,000 tests).

[143] 88 Fed. Reg. at 68012 (citing Anjeanette Damon, *The COVID Testing Company That Missed 96% of Cases*, PROPUBLICA (May 16, 2022), https://www.propublica.org/article/covid-testing-nevada-false-negatives-northshore).

[144] *See* CMS, *Survey of Northshore Clinical Laboratories, Inc.* (Dec. 29, 2021), https://s3.documentcloud.org/documents/21872905/northshore-clinical-labs-14d0426602-form-cms-2567-12292021.pdf.

positive."[145] As an analogy, a mammogram indicating risk of breast cancer is not "wrong" just because a biopsy or other follow-up testing reveals that the patient does not have breast cancer. The mammogram did its job: it selected a subset of patients who needed further evaluation. NIPS serve a similar purpose.

Moreover, NIPS are not "problematic" just because they identify many more patients at increased risk of carrying a fetus with a rare disease than the number of fetuses actually expected to be born with such disease. This is completely expected when screening large populations for extremely rare diseases, even when the test has near perfect sensitivity and specificity. To demonstrate, if a screening test has 99.9% sensitivity and specificity, then 1 out of every 1,000 patients without the condition would still be expected to receive a positive screening result. But if fewer than 1 in 1,000 patients in the population are expected to have the condition based on disease prevalence, then the number of positive screening results in patients without the condition would necessarily exceed the number of positive screening results in patients who actually have the condition. For example, when applied to DiGeorge Syndrome, which affects 1 in 4,000 births, the NIPS test would be expected to identify five times as many potential cases than there would be confirmed diagnoses. As acknowledged by the *New York Times* article cited by FDA, in a population of 20,000 pregnant patients, a test with 99.9% sensitivity and specificity—nearly perfect analytical validity—would be expected to identify 25 patients at higher risk of carrying a fetus with DiGeorge Syndrome, even though only 5 of those patients would be expected to receive a confirmed diagnosis.[146] These results are not an indication that the test is unreliable.

As with all screening tests, the goal of NIPS is to identify patients at elevated risk of a disease or condition, in this case, pregnancies with elevated risk of having chromosomal or genetic abnormalities. The tests are not meant to be diagnostic, and patients should not be using screening tests to make decisions without obtaining appropriate diagnostic testing. To revisit an earlier analogy, a physician would not recommend a mastectomy on the basis of a mammogram alone without confirmatory testing. If patients and providers are making decisions on the basis of screening tests alone, then there is a need for better education on the role of these tests.

Second, FDA's mischaracterization of NIPS ignores the significant public health benefits of these screening tests. Without a screening test, the only information a pregnant patient can obtain about the genetic health of their fetus must be obtained by invasive diagnostic procedures like chorionic villus sampling (CVS) and amniocentesis. Both methods require collection of cells or fluids proximal to the fetus and carry a risk of miscarriage.[147] Moreover, CVS generally is not performed until 10-12 weeks of pregnancy (and may require follow-up blood tests between 16-18 weeks of

---

[145] Indeed, this is the tradeoff for <u>all</u> screening tests. Screening tests will necessarily identify a greater number of patients with an elevated risk of having a particular condition than would be identified by a diagnostic test that identifies patients who definitively have a condition.

[146] Sarah Kliff & Aatish Bhatia, *When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong*, N.Y. TIMES (Jan. 1, 2022), https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html.

[147] Mayo Clinic, *Amniocentesis*, MAYOCLINIC.ORG, https://www.mayoclinic.org/tests-procedures/amniocentesis/about/pac-20392914 (last visited Nov. 3, 2023); Johns Hopkins Medicine, *Chorionic Villus Sampling (CVS)*, HOPKINSMEDICINE.ORG, https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/chorionic-villus-sampling-cvs (last visited Nov. 3, 2023).

pregnancy), and amniocentesis generally is not performed until 14-20 weeks of pregnancy.[148] In contrast, NIPS utilizes a blood draw taken from the expectant patient, making it non-invasive, and can be performed around 10 weeks of pregnancy.[149] NIPS is also a significant improvement over the previously available screening technology—maternal serum screening (MSS)—which, while noninvasive, generally is not performed until 15-22 weeks of pregnancy and reportedly identifies more patients than NIPS for follow-up diagnostic testing that ultimately receive a negative diagnostic result.[150] The availability of NIPS to screen for common chromosomal abnormalities can help a large majority of patients avoid more invasive tests like CVS and amniocentesis that have greater associated risks, including infection and miscarriage. Indeed, multiple studies have confirmed a significant reduction in invasive prenatal procedures since the introduction of NIPS.[151]

Studies have confirmed the technical performance and clinical validity of NIPS using cell-free DNA,[152] and current clinical guidelines recommend NIPS for pregnant patients. For example, the current guidance from the American College of Obstetricians and Gynecology (ACOG) recommends that prenatal genetic screening, including NIPS, as well as diagnostic testing should be discussed with **"all pregnant patients regardless of maternal age or risk of chromosomal**

---

[148] Mayo Clinic, *supra* note 147; Johns Hopkins Medicine, *supra* note 147.

[149] Society for Women's Health Research, *Understanding Genetic Screening and Maternal Care*, https://swhr.org/wp-content/uploads/2022/01/SWHR-Genetic-Screening-Poster-FINAL-2022Jan.pdf (last visited Nov. 3, 2023).

[150] John E Delzell, Jr., *What Can We Do To Prepare Patients for Test Results During Pregnancy?*, 173 WESTERN J. MED. 183 (2000), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1071060/; Mayo Clinic Laboratories, *Patient Education: Maternal Serum Screening*, MAYOCLINICLABS.COM, https://www.mayocliniclabs.com/-/media/it-mmfiles/Special%20Instructions/E/5/9/maternal%20serum%20screening%20patient%20information#:~:text=To%20receive%20maternal%20serum%20screening%20you%20must%20have,produced%20by%20the%20unborn%20baby%20and%2For%20the%20placenta (last visited Nov. 3, 2023); Illumina, *Comparing NIPT to other aneuploidy screening methods*, ILLUMINA.COM, https://www.illumina.com/clinical/reproductive-genetic-health/nipt/labs/nipt-vs-conventional-aneuploidy-screening.html (last visited Nov. 3, 2023).

[151] Sebastian Larion et al., *Association of Combined First-Trimester Screen and Noninvasive Prenatal Testing on Diagnostic Procedures*, 123 OBSTETRICS & GYNECOLOGY 1303 (2014), https://journals.lww.com/greenjournal/abstract/2014/06000/association_of_combined_first_trimester_screen_and.22.aspx; Kris Van Den Bogaert et al., *Outcome of Publicly Funded Nationwide First-Tier Noninvasive Prenatal Screening*, 23 Genetics in Med. 1137 (2021), https://www.gimjournal.org/article/S1098-3600(21)05214-X/fulltext; Lara A. Friel, Jennifer L. Czerwinski & Claire N. Singletary, *The Impact of Noninvasive Prenatal Testing on the Practice of Maternal-Fetal Medicine*, 31 AM. J. PERINATOLOGY 759 (2014), https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0033-1359717; Stephen J. Robson & Lisa Hui, *National Decline in Invasive Prenatal Diagnostic Procedures in Association with Uptake of Combined First Trimester and Cell-Free DNA Aneuploidy Screening*, 55 AUSTL. & N.Z. J. OBSTETRICS & GYNAECOLOGY 507 (2015), https://obgyn.onlinelibrary.wiley.com/doi/10.1111/ajo.12380.

[152] Nancy C. Rose et al., *Systematic Evidence-Based Review: The Application of Noninvasive Prenatal Screening Using Cell-Free DNA in General-Risk Pregnancies*, 24 GENETIC MED. 1379 (2022), https://www.gimjournal.org/article/S1098-3600(22)00714-6/fulltext.

abnormality," and among available screening options, "[c]ell-free DNA," i.e., NIPS, "is the most sensitive and specific screening test for the common fetal aneuploidies," though it is "**not equivalent to diagnostic testing**" (emphasis in original).[153] Notably, these guidelines supersede the 2012 ACOG statement that FDA cited in Reference 11 to the Proposed Rule, purportedly supporting that such tests should not, at that time, be used in the general, low-risk population.[154] Consistent with the available scientific evidence and clinical guidelines, payers have also recognized the value of NIPS and have made determinations that such tests yield useful and clinically valid information.[155]

3. FDA's characterization of oncology tests is inaccurate.

Finally, we are deeply disappointed in FDA's mischaracterization of LDTs developed and performed in the oncology field. Innovation in testing is of paramount importance to making advancements in the clinical care of oncology patients, but the Proposed Rule fails to recognize the important benefits of LDTs in this space. For example, long before there were any approved or cleared diagnostic test kits for evaluating genetic risk of developing certain hereditary cancers, high-complexity laboratories were developing and offering these tests, giving patients greater opportunity for clinical care. There are numerous examples of the lifesaving innovations pioneered by laboratories in this space. We noted several such examples in the prior sections: testing for BRCA mutations associated with breast and ovarian cancer, testing for KRAS mutations associated with non-small cell lung cancer, pancreatic ductal adenocarcinoma, and colorectal cancer, and NGS technology, more broadly. We also noted in prior sections how clinicians continue to rely on LDTs today to receive the most up-to-date information about their patients based on newly discovered and validated biomarkers.

Moreover, some of the references cited in the Proposed Rule regarding oncology LDTs are flawed and/or misconstrued. Two of the references warrant special attention: a study by Pfeifer et al. comparing reference samples (Reference 12 in the Proposed Rule) and the Friends of Cancer Research (FOCR) study on tumor mutational burden (TMB) LDTs (Reference 14 in the Proposed Rule).

First, the Proposed Rule cites a study by Pfeifer et al. that claims to have found that only 7 of 19 laboratories that tested the same samples with LDTs correctly reported all results.[156] This study

---

[153] ACOG, *NIPT Summary of Recommendations*, POLICY PRIORITIES: CURRENT ACOG GUIDANCE, https://www.acog.org/advocacy/policy-priorities/non-invasive-prenatal-testing/current-acog-guidance (last visited Nov. 3, 2023).

[154] *See* FDA, THE PUBLIC HEALTH EVIDENCE FOR FDA OVERSIGHT OF LABORATORY DEVELOPED TESTS: 20 CASE STUDIES (2015) http://web.archive.org/web/20151122235012/https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf.

[155] Andrew P. Dervan et al., *supra* note 68 ("All payers studied cover cfDNA screening for detection of trisomies 21, 18 and 13 in high risk, singleton pregnancies, based on robust clinical validity (CV) studies and modeled evidence of clinical utility (CU). … Starting in August 2015, 8 of the 19 payers also began covering cfDNA in average risk pregnancies, citing recent CV studies and updated professional guidelines."), https://www.nature.com/articles/gim2016145.pdf.

[156] 88 Fed. Reg. at 68011.

has been discredited, however. In late September 2023, the CAP Molecular Oncology Committee reanalyzed the data from this study, adjusting for confounding conditions, and found that "laboratories consistently have high detection rates" for the tested variants.[157] Moreover, based on this reanalysis, the results from the original study cited by FDA "are not generalizable to all molecular oncology testing and should not be used to market products or change policy affecting all molecular oncology testing."[158]

Second, FDA cites the FOCR study to imply that TMB LDTs are unreliable, claiming the study "found substantial variability among [TMB] tests manufactured by laboratories."[159] However, the data from such study actually support that inter-assay variability of TMB LDTs is comparable to the variability observed between FDA-authorized assays. Specifically, in addition to LDTs, the study included two FDA-authorized IVD assays, and while the study did not conduct pairwise comparisons of TMB results between assays, a preliminary analysis based on data provided in the FOCR publication shows similar, and in some cases greater, variability between the FDA-authorized assays than between the FDA-authorized assays and LDTs included in the study.

Moreover, FDA's naked assertion that the FOCR study showed empirical variability among test results fails to recognize the important scientific and clinical context in which such test results are interpreted. As noted in the publication, the empirical variability across assays was observed to increase with increasing TMB value. But TMB test results are only semi-quantitative, and above a specified cutoff there is limited to no clinical impact for the patient. Even a high degree of variability at TMB values well above the cutoff would have limited to no clinical impact because variability would not cause results to fall below the cutoff. Importantly, these cutoffs are assay-specific to account for each assay's unique performance characteristics. However, differences in assay-specific cutoffs were not addressed or reported in this study.

Furthermore, the study was neither designed nor conducted to evaluate whether there was any clinical impact of observed variability among TMB tests from different laboratories. Rather, the study was designed and conducted as a collaborative effort including IVD and LDT assay developers to identify sources of variability between assays, to develop recommendations on the design of TMB assays, and to support transparency with the goal of furthering community understanding of TMB assays and results. Using the study to imply that LDTs may not provide accurate or reliable results misrepresents the design and results of this study.

Finally, other evidence cited by FDA is anecdotal and presented without important context. In particular, the Proposed Rule cites "[a]n article published earlier this year [that] detailed an oncologist's experience with false results from an unapproved blood-based multi-cancer detection IVD offered as an LDT and intended to screen for more than 50 types of cancer (Ref. 16)."[160] As an initial matter, as in the context of NIPS, cancer screening results are not "false" just because a definitive diagnostic test yields a different result. But beyond that point, this summation of the

---

[157] Ahmet Zehir et al., *SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance*, ARCHIVES PATHOLOGY & LAB'Y MED. 1 (2023), https://meridian.allenpress.com/aplm/article/doi/10.5858/arpa.2023-0322-CP/496201/SPOT-Dx-Pilot-Reanalysis-and-College-of-American.

[158] *Id.*

[159] 88 Fed. Reg. at 68011.

[160] 88 Fed. Reg. at 68011.

reference leaves out important context about the analytical validity of the test at issue. The article tells the story of only one positive result in a patient determined not to have cancer, and one negative result in a patient who ultimately did have cancer. But as explained in the article, the oncologist in the story has encountered only one other "false positive" out of about 2000 test results in over 18 months, and "[s]he also discovered two positive signals for cancer … that were confirmed with follow-up tests," both of which were caught "remarkably early, in time for treatment."[161]

Finally, FDA itself has recognized the role that LDTs can play in informing treatment decisions in the oncology space. This past summer, FDA announced a pilot program that would allow certain oncology drugs that require companion diagnostics to be approved without a corresponding FDA-approved companion diagnostic.[162] Instead, FDA would publish information about the performance characteristics of the CTA used in clinical studies of the drug. With that information, laboratories would then be able to develop LDTs to inform patient treatment decisions.

For all of these reasons, FDA has mischaracterized LDTs in the preamble to the Proposed Rule. This faulty characterization cannot serve as the underlying rationale for imposing the ill-fitting device framework on LDTs. As discussed below, FDA's cost-benefit analysis for the Proposed Rule is also flawed and cannot support finalizing the Proposed Rule.

V. FDA's Cost-Benefit Analysis is Flawed in Numerous Ways and Cannot Support Finalizing the Proposed Rule.

FDA fails to grasp the impact that finalizing this proposed rule would have on laboratories, patients, and other stakeholders. ACLA strongly disagrees with the cost-benefit analysis in the Proposed Rule and the RIA. Below we summarize key points regarding how FDA (A) underestimates the costs of the Proposed Rule, and (B) overestimates the benefits of the Proposed Rule, that the Agency should consider and incorporate into any final regulatory impact assessment.

Additionally, as demonstrated by the analysis of Professor Chris Carrigan in Exhibit 1, FDA's economic assessment fails to adhere to the standards described in the academic literature as well as OMB's Circular A-4. These fundamental concerns result in an RIA that: 1) significantly understates costs by failing to quantify a key ancillary effect; 2) substantially inflates benefits by misusing benefit transfer methods; 3) provides limited ability to evaluate reasonable alternative regulatory approaches; and 4) offers minimal discussion of the distributional effects, including those on marginalized and underserved communities. ACLA incorporates by reference that analysis.

A. FDA underestimates the costs of the Proposed Rule.

Applying device regulation to LDTs, as proposed, would have significant negative impacts on the availability of tests that are available only as LDTs, innovation in diagnostic and laboratory science, and broader access to testing. However, FDA uses numerous assumptions and guesswork to derive its estimates of costs associated with the Proposed Rule. For an agency that seeks to ground its work in scientific analysis and robust evidence, this analysis is concerning.

---

[161] Donavyn Coffey, *Blood Test Positive for Cancer, but Is There Really a Tumor?*, MEDSCAPE (Feb. 17, 2023), https://www.medscape.com/viewarticle/988431.

[162] *See* FDA, *Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program* (June 21, 2023), https://www.fda.gov/medical-devices/in-vitro-diagnostics/oncology-drug-products-used-certain-in-vitro-diagnostics-pilot-program.

As an initial matter, FDA made no attempt to collect information about the number of high-complexity CLIA laboratories or LDTs currently being offered that would be affected by the Proposed Rule, despite the Agency having the tools to do so. For example, FDA could have coordinated with other HHS agencies, CMS and CDC, to collect information from CLIA-certified laboratories regarding the number of laboratories that are high-complexity laboratories and the number of LDTs offered by each such laboratory. Laboratories applying for CLIA-certification must submit Form CMS-116, which requires a list of the non-waived tests the laboratory will offer, including whether the test is moderate- or high-complexity.[163] FDA also could have issued an RFI seeking information regarding the number of high-complexity clinical laboratories and the number of LDTs currently being offered.

FDA did not do any of this. Instead, FDA has proposed rulemaking on the basis of anecdotal evidence and extrapolations about the potential impact to industry, patients and other stakeholders. Under the Administrative Procedure Act, the Agency "must examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983). Where (1) key data is readily available to an agency, or (2) certain data is critical to the agency's decision but the agency fails to either make an effort to collect that data or explain why it was unable to collect it, a court should find that the agency failed to "examine the relevant data and articulate a satisfactory explanation for its action." *See, e.g., Rural & Migrant Ministry v. EPA*, 565 F. Supp. 3d 578, 599–600 (S.D.N.Y. 2020); *Innovator Enterprises, Inc. v. Jones*, 28 F. Supp. 3d 14, 26 (D.D.C. 2014). This is not a scenario where the data is unobtainable, nor is there a valid reason for FDA not having the data. *See F.C.C. v. Fox Television Stations, Inc.*, 556 U.S. 502, 519 (2009) (explaining that there "are some propositions for which scant empirical evidence can be marshaled" and that "it is one thing to set aside agency action under the Administrative Procedure Act because of failure to adduce empirical data that can readily be obtained [and] something else to insist upon obtaining the unobtainable.").

As a result of FDA proceeding without data necessary to support its analysis, FDA has significantly underestimated the costs of complying with the Proposed Rule. As explained further below, this underestimate stems from a number of errors in FDA's analysis, including:

- Underestimating the number of affected laboratories, the number of LDTs that are currently available, and the number of LDTs that laboratories develop annually;
- Underestimating the number of currently available LDTs and new LDTs that would require different premarket submissions;
- Underestimating the cost of test validation and preparation of premarket submissions for LDTs; and
- Underestimating the cost of compliance with other device regulations for LDTs.

When these costs are more accurately estimated, the negative consequences for laboratories, patients, FDA, and other stakeholders are immense. As explained earlier in these comments, these

[163] Form CMS-116, *Clinical Laboratory Improvement Amendments (CLIA) Application for Certification* (12/21), https://www.cms.gov/medicare/cms-forms/cms-forms/downloads/cms116.pdf.

costs include removal of important tests from test menus due to the cost of compliance, and not due to any reliability or accuracy concerns; significant slow-down in diagnostic innovation by laboratories due to competing demands for limited resources; reduced testing capacity at laboratories due to competing demands for limited resources and potential closures of laboratories; and slower availability for innovative diagnostics due to constrained resources at FDA.

1. *FDA has underestimated the number of affected laboratories, the number of LDTs that are currently available, and the number of LDTs that laboratories develop annually.*

FDA has estimated there to be approximately 1,200[164] laboratories that would be affected by the Proposed Rule and that such laboratories offer, on average, 67 tests per laboratory, leading to an estimate of 80,400 tests potentially affected. FDA reached those estimates by extrapolations from the New York State database of tests, but publicly available sources support estimates that are higher. For example, in CMS's most recent update to the CLIAC, the agency reported 34,266 laboratories that have a certificate of compliance or accreditation, i.e., 34,266 laboratories that perform moderate- and/or high-complexity testing.[165] It is unlikely that only 3.5% of these laboratories perform high-complexity testing and offer LDTs, as suggested by FDA's estimates.

FDA's estimate of 67 tests per laboratory also is far too low. Several ACLA members report offering hundreds or even thousands of LDTs. And this number would align with other publicly available estimates of LDTs. For example, a paper by Halbisen and Lu in 2023[166] found that as of November 2022, there were a total of 37,106 genetic tests offered in the US for clinical purposes. The paper also estimates that in 2022, 3,097 new genetic tests were made available. Assuming that an equivalent number of new tests were first offered in 2023 (99.5% of which are clinical tests), the total estimate for genetic tests alone on the US market is 40,000 tests. This estimate is limited to genetic tests, almost all of which are offered as LDTs. FDA's estimate also does not account for LDTs that would continue to be introduced from now until whatever time that premarket submissions are required under any final phaseout policy, likely adding tens of thousands of additional tests.

Similarly, FDA has significantly underestimated the number of new LDTs that would become subject to regulation. FDA has estimated that 7,776 new LDTs would be offered each year, based on an estimated average of 6 new LDTs per laboratory per year, adjusted to account for LDTs offered by new laboratories. But as noted above, the Halbisen and Lu paper estimates that, for genetic tests alone, 3,097 new tests were made available in 2022.[167] Moreover, as the RIA acknowledges, some large reference laboratories may develop as many as 100 new LDTs per year. Further, adjustments and updates to FDA-regulated tests would trigger the need for new FDA submissions. FDA needs to account for this reality.

---

[164] For purpose of these comments, we rely on FDA's "primary" estimates throughout the RIA. But of course the RIA accounts for a range of costs.

[165] Gregg Brandush, *CMS CLIA Update, Division of Clinical Laboratory Improvement and Quality* (Nov. 9, 2023), https://www.cdc.gov/cliac/docs/november-2023/2_CMS_Update.pdf.

[166] *See* Alyssa L. Halbisen & Christine Y. Lu, *supra* note 122.

[167] *Id.*

2. FDA's estimates regarding premarket review are misguided.

With respect to LDTs that are currently offered, the Proposed Rule assumes that 4,210 tests would require a PMA Submission, 4,020 would require a De Novo, 32,160 would require a 510(k), and the rest would be exempt from premarket review. This is a significant underestimate across submission types. FDA's underestimate stems from several mistakes including: (1) underestimating the total number of LDTs that would require a premarket submission; (2) underestimating the ratio of LDTs that are novel and would require PMA approval or De Novo Classification; and (3) overestimating the ratio of LDTs that would be 510(k)-exempt.

First, as explained above, FDA has underestimated the number of currently available LDTs. Accordingly, even if FDA were correct that of all existing LDTs, only 5.2% would require PMA Submissions, only 5% would require De Novo requests, and only 40% would require 510(k)s, FDA would receive far more submissions—PMA Submissions, De Novos, and 510(k)s—than it anticipates.

Second, FDA has underestimated the number of LDTs that are novel and would require PMA approval or De Novo Classification. As discussed earlier in these comments, novel LDTs that lack a predicate device would require PMA approval or a De Novo classification because their technologies have surpassed that of FDA-cleared/approved devices, or because they are intended for a use for which there is no cleared/approved alternative. For example, as stated above, there are currently approximately 40,000 genetic LDTs currently available, and there are not currently available class I or class II genetic tests that could serve as predicate devices. The vast majority of these genetic LDTs would be required to undergo the PMA or De Novo process. Other testing methodologies rely entirely on LDTs. For example, as described above, virtually all mass spectrometry testing is done by LDTs.

The conclusion that most LDTs would require a PMA or De Novo is supported by FDA's own data. In the MDUFA V Fourth Quarter Performance report, the Agency reported that of 7 LDT submissions it received in FY2023, 5 were for PMAs, 1 was for a De Novo, and only 1 was for a 510(k).[168] Throughout the entirety of MDUFA IV, the Agency reported that of the 49 LDT submissions it received in FY2018 through FY2022, 28—over half—were PMAs, 10 were De Novos, and 11 were 510(k)s.[169]

Third, FDA also has overestimated the ratio of LDTs that would be 510(k)-exempt and, accordingly, significantly underestimated the number of LDTs that would require a premarket submission. FDA has estimated that 50% of LDTs would be 510(k)-exempt, but this is wrong. Only a small number of LDTs would fall within a 510(k) exemption. Rather, in most cases, a 510(k) submission or a PMA supplement would be required because the laboratory is offering a modified version of a cleared or approved IVD. For all of these reasons, FDA's estimates of 4,210 PMA Submissions, 4,020 De Novo applications, and 32,160 510(k) submissions for existing LDTs is dramatically understated.

FDA's estimates regarding new and modified LDTs that would be subject to premarket review on an ongoing basis suffer from similar flaws. ACLA disagrees with FDA's estimate that, each year,

---

[168] FDA, *Quarterly Update on Medical Device Performance Goals --- MDUFA V CDRH Performance Data --- Actions through 30 September 2023* (Nov. 16, 2023), https://www.fda.gov/media/173923/download?attachment.

[169] FDA, *MDUFA IV (FY 2018-2022) Performance Report* (Nov. 16, 2023), https://www.fda.gov/media/173924/download?attachment.

FDA would receive 407 PMA Submissions, 389 De Novo requests, and 3,110 510(k) submissions. This is based on an estimated 7,776 new LDTs per year, and as noted above, this is a significant underestimate. Even if FDA's estimated percentages were correct (5.2% PMA Submissions, 5% De Novos, and 40% 510(k)s), far more tests would require premarket submissions than estimated. But FDA is wrong about those estimates for the same reasons described above for existing tests. Accordingly, FDA would receive significantly more PMA Submissions and De Novos for novel tests that lack a predicate device, as well as 510(k)s for non-exempt tests.

3. FDA has underestimated the cost of test validation and preparation of premarket submissions for LDTs.

Moreover, FDA has grossly underestimated the costs of bringing an LDT through the premarket review process. FDA estimates that costs of preparing and submitting a premarket submission is approximately $4.38 million for a PMA, $564,674 for a De Novo Classification Request, and $274,930 for a 510(k) requiring a method comparison study or $526,182 for a 510(k) requiring a moderately complex clinical study. However, these estimates do not reflect the real-world costs of conducting additional studies to support premarket submissions, and other elements of the cost estimates are unrealistically low. Earlier in these comments, we discussed the significant challenges of conducting validation studies according to FDA's requirements to support clearance or approval of tests. But even if those challenges could be overcome, the costs of test validation and premarket submissions is significantly higher than FDA estimated in its RIA.

With respect to costs not reflected in FDA's estimates, preparation of submissions for existing tests would require laboratories to re-validate their existing tests because FDA's design controls under 21 CFR section 820.30 cannot be applied retroactively to an already-designed test. However, FDA's RIA falsely claims that in estimating the costs of PMA, 510(k) and De Novo requirements, it can "exclude[] costs that would already be part of compliance with the QS requirements under Stage 3, including costs of developing design controls,"[170] even though FDA's one-time cost assessment for compliance with QS requirements under Stage 3 does not account for these requirements. Specifically, although the one-time cost assessment for Stage 3 includes general design controls under 21 CFR section 820.30(a), it does not include design and development planning, design review, design verification, design transfer, design changes, or the design history file under 21 CFR section 820.30(b) through (j). All of these elements are required for a compliant quality system to support a PMA approval, De Novo classification, or 510(k) clearance. They are conspicuously missing from FDA's RIA, and they must be considered either under Stage 3 as part of the one-time annual cost of compliance with QS requirements or under Stages 4 and 5 as part of the cost for bringing a premarket submission to FDA.

Moreover, even if FDA exercised some flexibility with regard to leveraging existing validation studies, FDA's estimates do not consider the costs associated with conducting additional validation studies to satisfy FDA's expectations where those studies were not required under existing regulatory frameworks. As discussed earlier in these comments, FDA often requires additional validation data that laboratories and other reviewing entities (e.g., CLIA, CAP, New York State) have not determined to be necessary.

---

[170] FDA, PRELIMINARY REGULATORY IMPACT ANALYSIS; INITIAL REGULATORY FLEXIBILITY ANALYSIS; UNFUNDED MANDATES REFORM ACT ANALYSIS 76-77 (2023), https://www.fda.gov/media/172557/download?attachment ("RIA").

Other costs also are significantly underestimated. As just one example of many, FDA estimates that identifying a predicate device for a 510(k) would require only 1.5 hours, costing only $123.48. While that theoretically could have been true in the past and in the simplest of cases for an experienced regulatory professional, it would take laboratories inexperienced with FDA's regulatory regime much, *much* longer to identify an appropriate predicate today, especially in the context of FDA's evolving policies related to the 510(k) program. In particular, even if *a* predicate could be identified in a short amount of time, it would take much, much longer to identify a predicate device according to FDA's "best practices" as announced in draft guidance in September.[171] According to this draft guidance, it is not enough to identify a "valid" predicate; sponsors are expected to identify a valid predicate that: (1) has been cleared using "well-established methods," (2) continues to meet or exceed safety performance expectations, taking into account post-market reports of design-related malfunctions and adverse events, (3) does not have "unmitigated use-related or design-related safety issues," including consideration of FDA safety communications; and (4) is not subject to "an associated design-recall." Understanding these requirements, let alone applying them, would take significantly longer than 1.5 hours, even for a seasoned FDA regulatory professional.

FDA also underestimates the costs of conducting required clinical studies. The RIA estimates that clinical studies would cost approximately $2.83 million for a PMA, $311,553 for a De Novo Classification Request, and $314,065 for a 510(k). However, these clinical studies can be far more expensive. One ACLA member was required to pay $2,000 per sample for a colorectal test. Based on that cost, a single submission requiring 650 supporting samples at a cost of $2,000 for each sample would cost $1,300,000 just to obtain relevant samples.[172] And that cost does not include the numerous other costs associated with running clinical studies, preparing applications, interacting with FDA, and otherwise processing applications. FDA also fails to recognize that access to appropriate tissue samples and orthogonal test methods are severely limited for certain types of tests.

Other examples of underestimates of costs include FDA's estimates for preparing regulatory submissions and holding pre-submission meetings. FDA estimates that the total cost of preparing a regulatory submission for a De Novo Classification Request is only $124,998, failing to recognize the greater cost of the FY2024 user fee for such submission ($145,068). FDA also estimates the costs of pre-submission meetings with FDA are only $2,000 to $2,500 across submission types, but sponsors spend significant amounts of time preparing pre-submission requests, reviewing initial feedback from FDA, and preparing for and holding meetings with the Agency. Moreover, a novel assay may require *several* pre-submission meetings. FDA's suggestion that sponsors spend only $2,000 to $2,500 of time and resources to prepare for such meetings is a gross underestimate.

4. FDA has underestimated the cost of ongoing compliance with other aspects of device regulations.

Finally, FDA underestimates the costs of ongoing compliance with other aspects of device regulations, even when premarket submissions are not required. For Stage 1, FDA bases its cost estimate for complying with medical device reporting (MDR) requirements on the approach taken

---

[171] FDA, DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF: BEST PRACTICES FOR SELECTING A PREDICATE DEVICE TO SUPPORT A PREMARKET NOTIFICATION [510(K)] SUBMISSION (2023), https://www.fda.gov/media/171838/download.

[172] An estimate of 650 samples is based on FDA-approved assays in various clinical areas. For example, Roche's Elecys Phospho-Tau CSF assay was required to be clinically validated with 646 samples. Sample types such as cerebral spinal fluid would likely be far in excess of $2000/sample.

for its 2014 final rule on *Medical Device Reporting: Electronic Submission Requirements*, which is an inappropriate comparison. This rule revised existing postmarket medical device reporting requirements as applicable to manufacturers already familiar with MDR reporting requirements. Laboratories, however, would start from scratch. It would not be sufficient to modify existing SOPs. Wholly new SOPs for complaint evaluation and MDRs would be required and employees would need to be educated and trained on these procedures. FDA's cost estimate for complying with corrections and removals reporting requirements, based on its 2020 notice, *Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Medical Devices; Reports of Corrections and Removals*, suffers from the same flaw.

For Stage 2, FDA's cost estimates for complying with registration and listing, labeling, and investigational use requirements suffer from the same flaws as in Stage 1, plus additional complexities specific to the nature of LDTs. For example, FDA estimates that a general/operations manager would require 3 hours to complete registration and listing for a single establishment and the LDTs offered therein. However, before laboratories can list their LDTs, they first must complete a regulatory assessment of the likely classification of each LDT, i.e., determine whether any particular LDT is class I, class II, or class III, and determine within which classification regulation/product code the LDT fits. For laboratories inexperienced in FDA regulation and classification of medical devices, this would be a significant undertaking and require *far* more than 3 hours to complete for FDA's estimated 67 LDTs per laboratory. And such regulatory analysis would be extremely consequential, likely driving the laboratory's strategy for premarket submissions, to the extent submissions would be pursued. Accordingly, laboratories could not rush through such analysis to satisfy FDA's registration and listing requirements. Furthermore, FDA's tables outlining costs of registration and listing also do not appear to include the annual registration fee, which in FY2024 would be $7,653 *per laboratory*. There currently are no waivers or reductions for registration and listing fees for small establishments, businesses, or groups.

With respect to labeling, FDA estimates that a general/operations manager would require 20 hours to redesign existing labeling for LDTs to comply with labeling requirements. However, it is not clear—at all—what the labeling requirements are for LDTs. Because LDTs are not a product, they have no packaging to which a label could be applied, nor are there existing instructions for use beyond the laboratory's procedure manual. FDA has not addressed how laboratories are expected to comply with labeling requirements, and even if FDA forces out a draft guidance within a year after finalization of the Proposed Rule, laboratories would be left scrambling to figure out how to comply by Stage 2 of the phaseout policy. Furthermore, 20 hours is a gross underestimate of the time required to additionally design and implement new processes to meet the labeling controls requirements in 21 CFR Part 820.

FDA also dramatically underestimates the costs of complying with investigational use requirements. As an initial matter, FDA's estimate that only 6.75% of investigational LDTs would require an application for an investigational device exemption (IDE) is flawed. This assumption is based on (1) the number of IDE applications FDA currently receives divided by the number of IVD marketing submissions FDA ultimately receives, and (2) FDA's assumption that only 50% of LDTs would require a premarket submission. As discussed earlier, FDA's assumption that only 50% of LDTs would require a premarket submission is deeply flawed. Moreover, this estimate completely ignores clinical trial assays developed solely for the purpose of supporting drug/biological clinical trials, where those assays are never intended for commercialization as a diagnostic assay. For example, screening patients for trials often requires development of *several* CTAs by different laboratories across the country to identify sufficient eligible patients for enrollment. Where the assays affect treatment of patients in a clinical trial, an IDE application may be necessary for *each*

CTA, even though only *one* marketing submission for a companion diagnostic may ultimately be submitted. FDA has failed to consider these CTAs in its estimate.

Additionally, FDA's estimates of the costs of complying with investigational use requirements ignores the costs of complying with the abbreviated requirements for non-significant risk devices. FDA's estimate of costs applies only to those investigational LDTs that would require an IDE application. However, non-exempt investigational LDTs that are not significant risk also must comply with abbreviated requirements related to labeling, IRB approval, informed consent, monitoring, recordkeeping, and reporting.[173] FDA has failed to consider the costs of compliance for non-significant risk LDTs used in clinical trials.

FDA also has underestimated the costs of ongoing compliance associated with quality system requirements. Aligning current laboratory quality requirements under CLIA, CAP, international standards such as the International Organization for Standardization (ISO) 15189, New York State Department of Health, and other applicable state laws with a shifting FDA quality regime is a complex exercise. FDA estimates that establishing an FDA-compliant quality system would require only $60,466 per laboratory for one-time costs,[174] but this estimate fails to account for some of the most significant quality requirements related to design controls, purchasing controls and acceptance activities. Table 23 of the RIA lists the one-time annual requirements for establishing an FDA-compliant quality system, but it accounts only for "general" design controls under 21 CFR section 820.30(a) and does not account for any other design control requirements under 21 CFR sections 820.30(b) through (j), as discussed above, nor does it account for purchasing controls under 21 CFR section 820.50 or acceptance activities under 21 CFR sections 820.80 and 820.86.[175] All of these quality system requirements are fundamental to demonstrating that a device is manufactured consistent with FDA's quality requirements.[176] Accordingly, FDA's estimates for establishing a compliant quality system are deceivingly low.

Furthermore, FDA does not even attempt to quantify the costs of laboratories grappling with the shifting quality system requirements as FDA considers finalizing amendments to the quality system regulation to incorporate by reference the 2016 edition of ISO 13485, Medical devices – Quality management systems for regulatory purposes. Even if the requirements of this ISO are similar in some respects to the current quality system regulation under 21 CFR Part 820, shifting to

---

[173] *See* 21 CFR § 812.2(b)(1).

[174] Estimated based on dividing FDA's estimate for one-time costs ($72.56 million) over FDA's estimate of affected entities (1,200).

[175] RIA Table 29.

[176] One potential rationale for excluding these elements may be that they are particularly relevant to supporting a marketing submission (PMA, De Novo, or 510(k)) for a device, such that they should be considered part of the cost of pursuing marketing authorization for tests, but FDA expressly excludes the design control requirements from their cost estimates for compliance with Stages 4 and 5 of the phaseout policy. *See* RIA at 76-77 ("We have excluded costs that would already be part of compliance with the QS requirements under Stage 3, including costs of developing design controls, acquiring GMP-compliant manufacture capability, and developing a risk management system."). Moreover, including such costs only under Stages 4 and 5 would fail to recognize that compliance with these elements of the quality system also apply to 510(k)-exempt LDTs, which, by FDA's estimate, would account for 50% of LDTs. It would also fail to account for the cost of establishing and implementing an entire design control process, independent of any particular LDT.

this new standard in the midst of a regulatory overhaul for LDTs would necessarily increase the costs to laboratories attempting to establish an FDA-compliant quality system. For example, responsible laboratories acting expeditiously to establish a quality system under 21 CFR Part 820 would incur additional costs when the regulation changes to reference ISO 13485, and they are forced to revisit completed work to incorporate this changed standard. FDA has not considered the impact of this shifting regulation on the costs of compliance for laboratories.

B. The claimed benefits of the Proposed Rule are dramatically overstated.

FDA claims that the Proposed Rule would generate substantial benefits and cost savings. The Agency claims that FDA regulation of LDTs would alleviate misdiagnoses and incorrect treatments that result from LDTs, promote more timely diagnoses, and reduce legal costs associated with lawsuits. FDA's benefit calculations are entirely speculative, relying on a number of shaky assumptions and questionable analytic steps. Moreover, the underlying studies cited by the Agency to support its analysis are flawed and cannot be used to generalize across LDTs.

1. FDA's overall approach to calculating the benefits of the Proposed Rule is fundamentally flawed.

Before turning to the specific evidence cited by FDA in its benefit calculations, there are several overarching flaws in FDA's approach. As we discussed previously, the LDTs cited by FDA in its benefits calculation represent a vanishingly small fraction of the number of LDTs available today and relied upon by physicians. FDA could have begun this regulatory process by requesting data from the laboratory community on the performance of LDTs, so that a systematic or more representative analysis could have been included in the Proposed Rule and RIA. FDA chose not to do that. Instead, FDA opted to go forward with a Proposed Rule and RIA by selecting a handful of examples and then extrapolating those isolated examples to the entire laboratory community. Extrapolating claimed misdiagnoses – using cherrypicked examples, while simultaneously ignoring other evidence of high quality LDTs – is inappropriate. This raises the same concerns expressed above regarding FDA's failure to "examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983).

Further, although FDA pays lip service to the fact that no test is perfect, the analysis employed starts with the premise that if LDTs were regulated as devices, problems associated with inaccurate test results would all but evaporate. That is obviously not the case. No diagnostic test, whether offered as an LDT or offered as an FDA-approved or -cleared test, is 100% accurate. Stated differently, every test has a certain sensitivity and specificity, reflecting that false positives and false negatives are expected in some number of patients. These risks are unavoidable and well accepted. Depending on a variety of factors, the sensitivity and specificity may be relatively high (e.g., in some cases exceeding 99%), but in other cases, the sensitivity and specificity may be lower. FDA knows this. For example, in 2022, FDA cleared a De Novo application for an assay to detect kidney stress in patients at risk of acute kidney injury. In clinical validation studies, the data reflected the test's sensitivity ranged from 76% to 93% and the test's specificity ranged from 45% to 51%.[177] Notwithstanding that level of accuracy, FDA rightly concluded that the value of having this tool available to clinicians outweighed the potential for false negative and false positive results.

[177] *See* FDA, De Novo Decision Summary: DEN130031, https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130031.pdf (last visited Nov. 14, 2023).

Moreover, even when the sensitivity and specificity are quite high (e.g., 99%), such tests will necessarily yield a number of false results when the prevalence of a condition is extremely rare. Furthermore, there have been many recalls of FDA-approved or -cleared diagnostics for quality or other issues that impact the accuracy of those tests.[178]

Were FDA to conduct an impact analysis that uses only IVD kits with relatively high false positive/negative rates, IVDs for use in rare disease populations, and recalled devices, and then extrapolate those results to the entire IVD industry, the results would be poor. Such an analysis would likely conclude that FDA-approved or -cleared assays are causing innumerable harms to the health care industry and that a different FDA regulatory regime, assumed to cure all the claimed problems, would yield significant benefits. That would be a wholly inappropriate and unfair analysis. But that is exactly what FDA has done here. It has identified a small handful of LDTs, portrayed those examples in the worst light possible, extrapolated those results to the entire LDT community, and then made an assumption that FDA regulation would cure all faults. This is not a fair picture of LDTs and not an accurate picture of the benefits that could result from FDA regulation of LDTs as devices.

Finally, FDA's benefit calculations flow from claimed inaccuracies associated with LDTs and an assumption that each inaccurate result associated with an LDT leads to a misdiagnosis and/or inappropriate treatment decisions. But in virtually every case, diagnostic testing is used in connection with other assessment tools and clinical judgment. Again, FDA knows this. For example, the cleared intended use of the kidney stress test system cited above states that the test "is intended to be used in conjunction with clinical evaluation in patients who currently have or have had within the past 24 hours acute cardiovascular and or respiratory compromise and are ICU patients as an aid in the risk assessment for moderate or severe acute kidney injury (AKI) within 12 hours of patient assessment." In other words, clinicians should interpret the output of the diagnostic test in conjunction with other assessment and clinical judgment. LDTs are no different. Physicians and other clinicians must take the output of the test and consider it together with other resources and experience. The result of the assay is one input – usually amongst many inputs – used to decide on a course of treatment for a patient. FDA's analysis must account for this.

2. *FDA's estimates rely on flawed studies and examples.*

    a) The data and studies underlying FDA's estimate of expected reduction in misdiagnosis are flawed.

FDA estimates the probability of misdiagnosis from "problematic LDTs" by considering three probabilities: (1) the probability that a misdiagnosis occurs after testing with an IVD (as opposed to another method of diagnosis); (2) the probability that that an LDT was used in the diagnosis; and

[178] *See, e.g.*, FDA, *Remel, Inc. Recalls Thermo Scientific Gram Negative IVD AST Sensititre Plate for Risk of Potential False Susceptible Results*, https://www.fda.gov/medical-devices/medical-device-recalls/remel-inc-recalls-thermo-scientific-gram-negative-ivd-ast-sensititre-plate-risk-potential-false (last visited Nov. 11, 2023); FDA, *Class 2 Device Recall therascreen KRAS RGQ PCR Kit (24)*, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRes/res.cfm?id=203179 (last visited Nov. 11, 2023).

(3) the probability that the LDT was "problematic."[179] To the extent that these probabilities are supported by underlying studies (and one is not), those studies are flawed.

First, FDA assumes that "50% of misdiagnoses occur after testing" with an *in vitro* diagnostic test, presumably including both IVDs and LDTs. There is no data underlying this estimate. Moreover, as explained above, the result of the assay is one input – usually amongst many inputs – used to decide on a course of treatment for a patient. Even if a misdiagnosis occurs after use of a diagnostic test, it is wrong to attribute that misdiagnosis to the test alone.

Second, FDA significantly overestimates the probability that an LDT is used to diagnose a patient, and accordingly, overestimates how many misdiagnoses may be avoided if so-called "problematic" LDTs were removed from the market. In its RIA, FDA quotes a 2023 report from Grand View Research that "LDTs constitute about 50% of total *in vitro*-diagnostics devices that are used in some laboratories."[180] FDA then extrapolates this single statistic to estimate that "50% of IVDs are IVDs offered as LDTs." It is wrong to extrapolate this single statistic that applies only to "some laboratories," and it is also a gross overestimate based on other available data. Although there is a very high number of LDTs currently available and more are being developed every day, the ratio of LDTs versus IVDs performed in the clinical setting is significantly less than 50%. In a study by Rychert, et al., laboratory test orders at an academic medical center were reviewed to determine how frequently LDTs were ordered by clinicians.[181] The study found that of over 3 million tests ordered in a single year, only 116,583 (3.9%) were LDTs. The volume was higher in the cancer center compared with the university hospital (5.6% versus 3.6%, respectively), but nowhere near FDA's estimate of 50% of all tests ordered. The study also found this in the context of LDTs constituting a higher proportion of the distinct assays that were ordered. Of 1,954 distinct assays ordered over the course of the study, 880 (45%) were LDTs. This study supports that while there is a very high number of distinct LDTs that have been developed and innovated by laboratories, the rate at which they are used compared to IVDs is much lower than FDA estimates. Accordingly, FDA's estimates that 50% of diagnostic errors would be avoided by FDA regulation of LDTs is inaccurate and must be reassessed by the Agency.

Third, FDA has significantly overestimated the number of LDTs that are "problematic." FDA relies on the SPOT/Dx Pilot Publication authored by Pfeifer et. al from 2022, which FDA cites in support of the notion that 47% of LDTs are "problematic."[182] The SPOT/Dx pilot found that 9 out of 19 oncology LDTs had significantly lower performance than FDA-approved companion diagnostics. FDA then extrapolates that result to assert that there are potentially a significant number of deaths associated with preventable misdiagnoses due to problematic LDTs. Extrapolating yet further, FDA asserts that device regulation of such tests would prevent these misdiagnoses and would therefore result in savings of $27.7B (VSLY 3%). As an initial matter, it is inappropriate to use this single,

---

[179] RIA at 37. FDA considers a fourth probability, the probability of misdiagnosis being associated with a fatality, to calculate the annual fatalities due to misdiagnosis.

[180] RIA at 38 (citing GRAND VIEW RESEARCH, LABORATORY DEVELOPED TESTS MARKET SIZE, SHARE & TRENDS ANALYSIS REPORT BY TECHNOLOGY (IMMUNOASSAY, MOLECULAR DIAGNOSTICS), BY APPLICATION (ONCOLOGY, NUTRITIONAL & METABOLIC DISEASE), BY REGION, AND SEGMENT FORECASTS, 2023 – 2030 (2023)).

[181] Jenna Rychert et al., supra note 18.

[182] John D Pfeifer et al., *Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics,* 157 AM. J. CLINICAL PATHOLOGY 628 (2022).

small study to characterize the performance of all LDTs across multiple disciplines. But even if it were sound scientific practice to extrapolate from a single study (which it is not), relying on the Pfeifer study is not appropriate. A more recent analysis of the SPOT/Dx pilot data by Zehir et al., using proficiency testing methods, reached a fundamentally different conclusion.[183] Specifically, by adjusting for confounding variables, the reanalysis found that LDTs had comparable performance to FDA-regulated tests. Moreover, Zehir et al. also conducted an assessment of LDTs based on data from CAP proficiency testing programs and found that the overall detection rates for single nucleotide variants (SNVs) and multinucleotide variants (MNVs) were 97.2% (2,671 of 2,748) and 91.8% (1,853 of 2,019), respectively. The paper concludes that "CAP PT program data demonstrate that laboratories consistently have high detection rates for KRAS and NRAS variants." In addition, the authors warn that the "SPOT/Dx pilot results are not generalizable to all molecular oncology testing and should not be used to market products or change policy affecting all molecular oncology testing."

b) The examples on which FDA relies to extract claimed benefits from regulating LDTs are flawed.

In addition, FDA's RIA attempts to extract supposed benefits of regulating LDTs from isolated problems with COVID tests. As we have previously noted, FDA's Proposed Rule dramatically distorts the COVID experience and the role that laboratories played throughout the pandemic. FDA's RIA again cites its flawed analysis of the first 125 COVID EUA requests submitted to FDA. As we have discussed above, it is wholly misleading for FDA to use the first EUA requests – submitted in rush of activity in order to contribute to the public health, often before relevant guidance from FDA was available – as a basis for evaluating COVID tests more broadly, much less for evaluating LDTs more broadly. But in its RIA, FDA takes it a step farther. FDA refers to a single LDT for COVID offered in Chicago. But as FDA well knows, it is impossible to extrapolate that single test to a broader basis to evaluate LDTs. Moreover, the laboratory at the center of this story engaged in fraud and was out of compliance with CLIA. Even if the laboratory leveraged only cleared and approved IVDs, the results would likely have been the same. FDA regulation would not have changed the outcome.

The other examples that FDA relies on for claimed benefits suffer from similar flaws. For example, FDA points to a single laboratory test called StatinCheck that, in FDA's view, lacked clinical validity, and NIPS tests. FDA fails to explain why the StatinCheck test lacks clinical validity, making an evaluation of FDA's claimed benefits impossible. Similarly, FDA cites NIPS tests and potential issues with false positive results associated with rare variants. As we previously noted, FDA has the NIPS story exactly backward. Laboratories that pioneered NIPS testing should be lauded for their remarkable contribution to the public health and reducing health care costs. Prior to NIPS, women would either skip the screening step and proceed directly to invasive diagnostic tests that are associated with higher incidence of adverse events and higher costs or they would proceed first with a different screening method that identified far more women for follow-up, invasive diagnostic testing than identified through NIPS. NIPS is highly accurate and has reduced the rate at which women routinely seek invasive diagnostic testing, thus reducing the number of women unnecessarily exposed to such risks.[184] Although it is true that certain very rare variants are associated with false

[183] Ahmet Zehir et al., *supra* note 157.

[184] *See, e.g.*, Rifat Mokhtar et al., *Comparing Non-invasive Prenatal Testing With Invasive Testing for the Detection of Trisomy 21*, 14 CUREUS e31252 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9733793/ ("The high performance and effectiveness of NIPT are undeniable.").

positive results, that is a necessary function of ensuring that such tests have sufficient sensitivity to detect true positive rare variants. This is why NIPS are not intended as definitive diagnostic tests for such rare diseases and should not be used in that way. But the fundamental point is that NIPS tests have advanced the public health immeasurably. It is improper for FDA to ignore the obvious benefits of LDTs that are offered as NIPS.

3. FDA's analysis excludes studies showing the value of LDTs.

FDA ignores other studies demonstrating that LDTs perform at least as well as FDA-approved or -cleared IVDs. For example, a 2017 study by Kim et al.,[185] compared the performance of LDTs and FDA-approved assays for key biomarkers used for companion diagnostics, including BRAF, EGFR, and KRAS mutations. That analysis found that in "6,897 proficiency testing responses, both LDTs and FDA-CDx exceed 97% accuracy combined across all comparable molecular oncology proficiency testing samples." The study concluded that "[t]hese findings support both the excellent and equivalent performance of both LDTs and FDA-CDx in clinical diagnostic testing." Further, the study observed that many laboratories using FDA approved CDx modified those tests to "allow for more clinical practice variety."

Other recent studies have affirmed the value of LDTs in improving care and saving lives. As one example, in 2021, Dimmock et al. published the results of "Project Baby Bear," which evaluated the benefits of implementing whole genome screening protocols in five California hospitals.[186] Specifically, acutely ill patients who were less than one year old and within one week of hospitalization or had just developed an abnormal response to therapy, were screened by an LDT using rWGS-based rapid precision medicine (RPM). The study evaluated two prespecified primary outcomes—changes in medical care because of rWGS results and changes in the cost of care because of rWGS at 4 months, 12 months, and 18 years after return of results. The results were clear – rWGS proved to be a valuable tool in clinical decision making. Of the 184 babies whose DNA was sequenced in this project, rare genetic diseases that explained the infant's admission were diagnosed in 74 babies (40%), genetic variants of uncertain significance (VUSs) were identified in 21 babies (11%), and no diagnosis was made in 89 babies (48%). Most diagnoses were of very rare disorders that would not be expected to have been seen by the child's providers previously in their careers. The authors of the paper concluded that "the five-site quality improvement project known as Project Baby Bear developed a real-world system for the rapid delivery of whole-genome sequencing that improved outcomes and decreased costs of care. This project has demonstrated that hospitals and payors with similar systems of rapid precision medicine can deploy rWGS for critically ill children in a cost-effective manner."

As the above discussion and examples illustrate, the Proposed Rule and RIA cherry-pick allegedly poor performing tests in an effort to extrapolate significant economic benefits from FDA regulation of LDTs. But this is not an accurate picture. There are numerous LDTs that perform as well as, or better than, FDA regulated tests and that yield significant benefits. In subjecting these high performing LDTs to device regulation, FDA is imposing costs without any corresponding benefit to the public health. And in imposing such costs on high performing tests, FDA would deprive laboratories of resources needed to continue to develop novel diagnostics. FDA's Proposed Rule currently ignores this reality.

---

[185] Annette S. Kim et al., *supra* note 52.

[186] *See* David Dimmock et al., *supra* note 107.

4. FDA's Proposed Rule would not reduce litigation costs for laboratories.

FDA also claims that compliance with FDA regulations may reduce the incidence of litigation. In fact, subjecting laboratories to regulation as device manufacturers could potentially increase legal exposure under product liability law (although this would turn on the law of each state). For LDTs approved under PMAs, federal preemption may be available to mitigate the risks of product liability suits.[187] But according to FDA's estimates, only a small fraction of LDTs would be subject to PMA requirements. Further, there is no shortage of litigation associated with FDA-regulated devices, so there is no basis for FDA to assume FDA regulation would somehow decrease lawsuits associated with LDTs.

VI. The Proposed Rule Raises Significant Legal Concerns.

As the foregoing sections make clear, FDA should not go forward with the Proposed Rule because it is a bad policy choice. Subjecting LDTs to device law would harm the public health in numerous ways. But there is an even more fundamental reason that FDA should not go forward: finalizing the Proposed Rule would exceed the authority granted to FDA by Congress and would raise serious constitutional concerns. As discussed at the beginning of these comments, although FDA has claimed at various points over the last 30 years that it has authority to regulate LDTs as devices, it has never exercised that claimed authority in a comprehensive manner in the 85 years it had authority over devices. Instead, clinical laboratories developing LDTs have been regulated under a separate statutory and regulatory regime – CLIA – and complementary state laws. FDA is steering out of its lane in attempting to exercise jurisdiction over LDTs, with dangerous consequences for the public health.

A. LDTs are not "devices" under the FDCA.

In enacting the FDCA, Congress provided FDA with authority to regulate discrete categories of products. Each category of products – whether it be drugs, biologics, devices, or other product types – is subject to specific statutory definition. As explained below, LDTs are not devices according to the plain text of the FDCA. That conclusion is confirmed by the legislative history of the FDCA, which shows that Congress rejected a more expansive definition of the term, and by Congress's later enactment of CLIA, which established a regulatory framework for laboratories that develop and perform LDTs, and pursuant to which laboratories have been operating for 35 years (55 for laboratories subject to the original Clinical Laboratory Improvement Act of 1967). Furthermore, other provisions of the FDCA and FDA regulations confirm that LDTs do not become devices simply because they use devices. If Congress intended to provide FDA with authority to regulate LDTs as devices under the FDCA, it would have done so clearly.

1. LDTs are not "devices" according to the plain text of the FDCA.

Categorizing LDTs as "devices" would be inconsistent with the FDCA's plain text because LDTs are not physical objects. Under FDCA § 201(h), the definition of "device" comprises only physical objects, including "[a]n instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is … intended for use in the diagnosis of disease or other conditions". LDTs are not physical

[187] *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008).

objects. LDTs are methods of using various tools and devices to derive information relevant to a treatment decision to be made by a medical professional and patient. FDA's repeated insistence that an LDT is a device reflects a deep and fundamental misunderstanding of the nature of LDTs, as we described in depth earlier in these comments.

FDA's contention that an LDT is an "apparatus," "contrivance," or "article" that is "similar or related to" "instrument[s]" and "*in vitro* reagent[s]," 88 FR 68,017, cannot be squared with the fact that LDTs are not particular material things (or simply particular combinations of material things), but rather are services. Canons of statutory construction dictate that "words grouped together in a list should be given related meaning." *Dole v. United Steelworkers of Am.*, 494 U.S. 26, 36 (1990). Here, in common usage, the other terms listed in the definition of "devices" (instrument, implement, machine, implant, *in vitro* reagent) are all tangible objects, and thus the terms "apparatus" and "contrivance" should likewise be given that meaning. This conclusion is bolstered by the term "article" as a catch-all at the end of the list. The Oxford English Dictionary defines "article" as a "particular material thing, esp. one belonging to a specified class; a commodity; an item of goods or property." *Article*, oed.com, https://www.oed.com/dictionary/article_n?tab=meaning_and_use#38461235 (last visited November 6, 2023). Consistent with this definition, courts have consistently construed the term "article" to mean "material things. *See, e.g.*, *ClearCorrect Operating, LLC v. Int'l Trade Comm'n*, 810 F.3d 1283, 1291 (Fed. Cir. 2015) (construing the term "articles," in accordance with its "ordinary or natural meaning," in the Tariff Act to mean material things, and thus the term did not cover electronically transmitted digital data); *ClearCorrect Operating, LLC v. Int'l Trade Comm'n*, 819 F.3d 1334, 1336-37 (Fed. Cir. 2016) (finding the panel majority was correct in interpreting the word "articles" in section 337 to mean "material things" where that interpretation is mandated by the plain meaning of the word, the context of the statute and entire statutory scheme, and the legislative history).

The conclusion that "devices" include only physical products is consistent with the many other provisions of the FDCA that require the presence of an object, e.g., shipment and receipt in interstate commerce, commercial distribution, and holding for sale. Other provisions of the FDCA discuss devices in ways that only make sense if applied to physical products, like the requirement to repair, replace, or refund the purchase price of a device under section 518(b). The frequency of such statutory references is a powerful confirmation that Congress understood "devices" to encompass only tangible products and not intangible professional services. Several of FDA's promulgated regulations for devices similarly can only be understood when applied to a tangible product. Unlike devices, LDTs cannot be packaged or affixed with a label that bears a unique device identifier. *See* 21 CFR Part 801. Additionally, FDA's quality system regulation defines the word "product" to include "in-process devices, finished devices, and returned devices." 21 CFR § 820.3(r). Clinical laboratories may use articles to develop and perform LDTs, but that does not transform LDTs into articles themselves.

Moreover, the term "*in vitro* reagent" does not include LDTs because an LDT is not an *in vitro* reagent. An *in vitro* reagent is a chemical or mixture used to elicit a chemical reaction. *See, e.g.* 21 CFR §§ 809.10(a) (requiring the label of an IVD that is a "reagent" to include its name, "quantity, proportion or concentration", as well as "storage instructions adequate to protect the stability of the product," and "a declaration of the net quantity of contents"); 809.10(d) (describing the labeling for "general purpose laboratory reagents (e.g., hydrochloric acid)"); 809.10(e) (describing the labeling for "analyte specific reagents (e.g., monoclonal antibodies, deoxyribonucleic acid (DNA) probes, viral antigens, ligands)"). *In vitro* reagents are one component used in diagnostic tests, but they are not the tests themselves. The fact that Congress gave FDA authority over one

discrete article used to perform an LDT does not equate to Congress giving FDA authority over LDTs themselves.

Finally, LDTs did not become devices just because they have become more sophisticated. FDA asserts in the Proposed Rule that regulation is justified because LDTs have become more complex and are used to screen or diagnose complex and important medical conditions. However, FDA cannot justify applying device regulation to LDTs that are not within FDA's jurisdiction for devices. If FDA believes that any market changes could justify regulation of some LDTs but not others, then the burden is on the Agency to explain why those changes make a difference under the statute, i.e., why those changes mean that certain LDTs are devices, as defined in the FDCA. LDTs do not meet the definition of a device, and the fact that modern LDTs have become more advanced or that LDTs screen/diagnose important diseases does nothing to change that conclusion.

2. The legislative history of the Medical Device Amendments and CLIA confirm that LDTs are not "devices" under the FDCA.

Because the text of the FDCA makes it clear that LDTs are not devices, it is not necessary to consider legislative history. *See, e.g., Mohamad v. Palestinian Auth.*, 566 U.S. 449, 458-59 (2012). Nevertheless, in this situation, the legislative history of the FDCA and CLIA only strengthens the conclusion that LDTs are not devices.

a) Congress rejected a broader definition of "device" when enacting the MDA.

The legislative history of the Medical Device Amendments of 1976 (MDA) is consistent with the reading that devices are physical objects and, accordingly, do not include LDTs. Congress's Conference Report on the bill refers to devices as "products" and "articles." H.R. Rep. No. 94-1090, at 62, 65 (1976) (Conf. Rep.). The House Report also refers to devices as "products," "machines," and "articles." H.R. Rep. No. 94-853, at 6 (1976). Moreover, the House Report notes that, "generally the term 'device' is used in the bill to refer to an individual product or to a type or class of products," except where one device is indicated for multiple intended uses. *Id.* at 14. Finally, the Senate Report stated that the bill carefully defined "device" so as to specifically include implants, *in vitro* diagnostic products, and other similar or related articles. S. Rep. No. 94-33, at 17 (1975). FDA points to the use of the term "diagnostic service" in a Senate Report that accompanied an earlier iteration of the bill, *see* 88 Fed. Reg. 68,018, but what Congress referred to as "devices" were "diagnostic products," and the "device" described in the example discussed by the Report was a "diagnostic machine, the 'Radioscope.'" S. Rep. No. 93-670, at 3–4 (1974) ("One popular area for quack devices has been ***diagnostic products***. During the 1950's, the biggest source of ***such devices*** was the Electronic Medical Foundation of San Francisco.... There were estimated to be about 5,000 of the ***devices*** [a diagnostic machine called the Radioscope] throughout the country.... The blood-spotted paper was put into a slot of the electrical ***device*** called the 'Radioscope' while the operator stroked with a wand the abdomen of a person holding metal plates connected to the ***device***.") (emphasis added).

In adopting the definition of "device" at section 201(h) that is limited to articles, Congress rejected a more expansive definition that would have included "systems." As FDA points out in the preamble to the Proposed Rule, the regulations for "in vitro diagnostic product" at 21 CFR Part 809 refer to such products as "systems" and "test systems," and FDA repeatedly asserts that LDTs are "devices" because they are "test systems." 88 FR 68,017–19. But these regulations for *in vitro* diagnostic products, and particularly the definition of *in vitro* diagnostic product at 21 CFR § 809.3, were promulgated before the 1976 Medical Device Amendments. Reorganization, Republication and Recodification, *Title 21—Food and Drugs, Chapter I—Food and Drug Administration, Department*

of Health, Education, and Welfare, Subchapter H—Medical Devices, 41 Fed. Reg. 6896 (Feb. 13, 1976) (making a nonsubstantive change to reorganize and move the definition of "in vitro diagnostic product" from 21 CFR 328.3 to 21 CFR 809.3, prior to enactment of the Medical Device Amendments on May 28, 1976). And when the MDA was enacted, "device" was defined to include neither the term "test system" nor "system." Congress did not adopt that wording in 1976 or at any time since, further buttressing the fact that FDA's reliance on that regulation or the concept of a "test system" is misplaced.

FDA also has previously asserted that the addition of "*in vitro* reagents" into § 201(h) was intended to capture LDTs, but that is not so. *See* FDA, *Draft Guidance: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)*, at 5 (Oct. 3, 2014). As an initial matter, as explained above, an LDT is not an *in vitro* reagent. Moreover, the legislative history of the MDA makes clear that the addition of items to the list of articles qualifying as devices—including *in vitro* reagents—did not expand the device definition beyond tangible articles. The House Report explains that "[t]he new definition retains (in somewhat more precise detail) provisions of existing law that a device is an article or component thereof," while making changes to distinguish drugs and devices by reference to chemical action and metabolism. H.R. Rep. No. 94-853, at 14.

b) Congress's subsequent enactment of CLIA confirms that LDTs are not "devices" under the FDCA.

Twelve years after Congress established FDA's device authority in the MDA, Congress passed the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which strengthened and transformed the regulatory scheme applicable to clinical laboratories, including those performing LDTs. Neither CLIA nor its legislative history acknowledges any then-existing FDA authority to regulate LDTs. The enactment of CLIA was driven in part by the desire for greater oversight over Pap testing, which was performed entirely by LDTs. *See* H.R. Rep. No. 100-899, at 16 ("Evidence was presented to the Committee that, in many laboratories, high numbers of false negative results were being reported. At the least, women have been given a false sense of security and discouraged from seeking proper care."). Sen. Rep. No. 100-561 at 5 ("Screening for cervical cancer through use of the Pap smear is the most common type of cytological examination. ... Unfortunately, there is much evidence of seriously inadequate performance by laboratories doing cytological testing."). At the time, FDA had not cleared or approved any devices for Pap tests to screen women for cervical cancer. However, there was no discussion of FDA oversight for Pap tests or cervical cancer screening in the legislative history of CLIA. Nor were there any Congressional inquiries into FDA regarding a derogation of its responsibilities regarding such tests. Surely, if regulation of LDTs, such as Pap tests, were an FDA responsibility, there would have been an outcry that FDA had abdicated its responsibility to protect the public health. In stark contrast, FDA's responsibility to regulate LDTs was not mentioned at all. What is more, the House Report stated that laboratories "were governed by two separate and distinct statutes, Medicare and CLIA"—not the FDCA—and the Report's section on the "Current Regulatory System" does not even mention FDA. H.R. Rep. No. 100-899, at 11-12 (1988).

Moreover, in enacting CLIA, Congress established a set of detailed requirements for laboratories that are entirely separate from the FDCA's requirements for device manufacturers. For example, rather than requiring clinical laboratories to register and list under FDCA § 510(c), laboratories must obtain a certificate prior to soliciting or accepting specimens for laboratory examinations or procedures under PHSA § 353(b). In addition, rather than requiring clinical laboratories to comply with good manufacturing practices (GMP) or the quality system regulation

(QSR) to ensure that LDTs are valid and reliable, CLIA requires laboratories to: (1) maintain adequate quality control and quality assurance programs to assure the "validity and reliability" of the tests and "the proper collection, transportation, and storage of specimens and the reporting of results," PHSA § 353(f)(1)(A); and (2) participate in regular proficiency testing, PHSA § 353(f)(1)(D) & (f)(3). CLIA also established a framework according to which states could enact their own clinical laboratory laws, and if such laws were "equal to or more stringent" than the requirements under CLIA, clinical laboratories in such state could be exempt from CLIA. 42 U.S.C. § 263a(p)(2). Two states have obtained such CLIA-exempt status—Washington and New York—and one of those states (New York) expressly reviews and approves LDTs.

Furthermore, CMS regulations expressly distinguish between laboratory tests that are cleared or approved by the FDA and those that are not. Under 42 C.F.R. § 493.1253(b)(2), laboratories must establish performance specifications prior to reporting results from a "modifie[d] … FDA-cleared or approved test system, or … a test system ***not subject to FDA clearance or approval*** (including ***methods*** developed in-house and standardized ***methods*** such as text book procedures) …" (emphasis added). These performance specifications include accuracy, precision, analytical sensitivity, analytical specificity to include interfering substances, reportable range of test results for the test system, reference intervals (normal values), and any other performance characteristic required for test performance. 42 C.F.R. § 493.1253(b)(2). CMS's recognition that there are "test system[s] not subject to FDA clearance or approval" is fully consistent with Congress's understanding in enacting CLIA that such test systems were not "devices" regulated by FDA.

Because Congress did not consider FDA as having authority to regulate laboratories, applying FDA authorities in addition to CLIA would introduce inconsistencies into the regulation of LDTs. FDA promotional requirements restrict the information that a device manufacturer can share about a regulated device. *See, e.g.*, 21 C.F.R. § 801.6 (misleading statements); 21 C.F.R. § 807.97 (misbranding by reference to premarket notification). However, CLIA requires laboratories to offer consultation on interpreting test results for specific patient conditions. *See* 42 CFR § 493.1445(e)(9) (requiring the laboratory director to "[e]nsure that consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific patient conditions"). Likewise, FDA requires a manufacturer to obtain approval or clearance for labeling changes to devices, but CLIA requires laboratories to provide pertinent updates on testing information as soon as it is available. *See* 42 CFR § 493.1291(e) ("Pertinent updates on testing information must be provided to clients whenever changes occur that affect the test results or interpretation of test results."). The CLIA requirements that permit licensed pathologists to share interpretive and off-label information regarding tests performed in their laboratories is consistent with the right of such pathologists to practice medicine within the scope of their licenses. FDA restrictions on providing such interpretive and off-label information, on the other hand, would limit such pathologists' ability to practice medicine within the scope of their licenses.

Congress's enactment of a regulatory structure for clinical laboratories that is inconsistent with FDA regulation of LDTs as devices precludes FDA from asserting jurisdiction over LDTs. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125–26 (2000).[188]

[188] In addition to enacting a different regulatory scheme for laboratories and LDTs in CLIA, Congress has established reimbursement systems for diagnostic tests that results in coverage and payment for tests that are (continued…)

3. LDTs do not become devices because they use devices.

LDTs do not become devices just because devices are used in performing an LDT. This is recognized in FDA regulations. Specifically, FDA regulations do not require a person providing a service with a device to be the manufacturer of the device, and therefore, no premarket review is required for the device used by the person. For example, 21 C.F.R. § 807.65(i) exempts from registration "[p]ersons … whose major responsibility is to render a service necessary to provide the consumer (i.e., patient, physician, layman, etc.) with … the benefits to be derived from the use of a device; for example, a … clinical laboratory … whose primary responsibility to the ultimate consumer is to … provide a service through the use of a previously manufactured device." Under section 510(k) of the FDCA and 21 C.F.R. § 807.81(a), FDA's premarket requirements apply only to "[e]ach person who is required to register" an establishment. Because clinical laboratories are not required to register, they are not required to submit premarket notifications for the testing services they offer. Thus, FDA's regulatory framework already recognizes that services performed with devices are not themselves devices.

B. Had Congress provided FDA with authority over LDTs, it would have done so expressly.

Under the "major questions doctrine," as recently cemented by the Supreme Court in *West Virginia v. EPA*, 142 S. Ct. 2587 (2022), courts require "something more than a merely plausible textual basis" when an agency asserts "sweeping and consequential authority." *Id.* at 2608–09. The seminal "major questions" case is *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000), where the Court rejected FDA's claim that its "drug" and "device" authority gave it the power to regulate tobacco products, concluding that "Congress could not have intended to delegate [authority] of such economic and political significance … in so cryptic a fashion." *Id.* at 160. The Court also reasoned that "FDCA's overall regulatory scheme," "subsequent tobacco-specific legislation," and Congress's rejection of legislative proposals to give the FDA jurisdiction over tobacco all indicated that the FDA was precluded from regulating tobacco products. *Id.* at 159–61.

LDTs represent a longstanding, significant part of the U.S. healthcare system and play a critical role in delivering dynamic healthcare solutions to patients. Yet with no express statutory authorization, FDA has proposed to regulate this important sector in a manner that would fundamentally alter the market. As in *Brown & Williamson*, it is implausible that Congress chose to delegate to FDA an issue of "such economic and political significance … in so cryptic a fashion." 529 U.S. at 160. The Supreme Court has recently and repeatedly counseled that federal agencies should "hesitate before concluding that Congress meant to confer [rulemaking] authority" regarding issues of vast "economic and political significance" where the statutory basis for such a regulatory action is unclear. *See West Virginia v. EPA*, 142 S. Ct. 2587, 2595 (2022); *King v. Burwell*, 576 U.S. 473, 485–86 (2015); *Utility Air Reg. Grp. v. EPA*, 573 U.S. 302, 324 (2014). The Proposed Rule runs directly contrary to that admonition. FDA relies on a strained interpretation of "device" that is not grounded in text or legislative history and that would have major consequences, not only economically but also

---

not subject to FDA clearance or approval. For example, for local coverage determinations for molecular diagnostic tests, in several regions across the country, CMS relies on Palmetto GBA's MolDX Program to determine coverage for both LDTs and for FDA-cleared or -approved tests. Also, Sec. 216 of the Protecting Access to Medicare Act, which established a new payment system for laboratory tests, defines an "advanced diagnostic laboratory test" to include a test that is neither approved nor cleared by FDA. *See* 42 U.S.C. § 1395m-1(d)(5).

for health care across the United States. The definition of "device" was not drafted with the understanding that it could be used to regulate a service in this manner. Additionally, as in *Brown & Williamson*, the overall FDCA regulatory scheme, as detailed below at V.C-D, and subsequent legislation specific to clinical laboratories, as detailed above at V.A.2.b, evince a Congressional understanding that LDTs do not fall within the FDCA's scope. Finally, Congress has considered—and has so far declined to enact—legislation that *would* have given FDA authority to regulate LDTs. *See* H.R. 8616 – VALID Act of 2022 (117th Cong.); H.R. 4128 – VALID Act of 2021 (117th Cong.). *See West Virginia*, 142 S. Ct. at 2614. Given its lack of statutory basis, FDA should not suppose that it has the power to regulate LDTs in this manner.

C. LDTs cannot be subject to any FDCA authorities that require devices to be introduced or delivered into interstate commerce for commercial distribution.

Looking beyond the FDCA's "device" definition to other provisions of the statute confirms that the FDCA's device authorities clearly were not intended to cover LDTs. To start with, many of FDA's authorities to regulate devices require that devices be introduced or delivered for introduction into interstate commerce for commercial distribution. *See, e.g.*, FDCA §§ 510(k) ("Each person who is required to register under this section and who proposes to begin the *introduction or delivery for introduction* into interstate commerce *for commercial distribution* of a device intended for human use shall, at least ninety days *before making such introduction or delivery*, report to the Secretary … action taken by such person to comply with requirements under section 514 [related to performance standards] or 515 [related to premarket approval] which are applicable to the device.") (emphasis added); 515(b)(1) (explaining that the Secretary must require premarket approval when a class III device "was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976," "is of a type so introduced or delivered," and "is substantially equivalent to another device within that type[.]"); 518(a)(1) (triggering notification requirements when the Secretary determines that, among other things, "a device intended for human use which is introduced or delivered for introduction into interstate commerce for commercial distribution presents an unreasonable risk of substantial harm to the public health[.]"). But LDTs are not, and indeed cannot be, introduced or delivered for introduction into interstate commerce for commercial distribution.

The FDCA defines "interstate commerce" as "(1) commerce between any State or Territory and any place outside thereof, and (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body." 21 U.S.C. § 321(b). But "[t]he typical LDT … never physically leaves the laboratory. There is no 'introduction' and no 'delivery.'"[189] That is because LDTs are "intended for clinical use and designed … [to be] used within a single laboratory[.]" Citizen Petition Denial Response from FDA CDRH to ACLA re: Docket No. FDA-2013-P-0667 at 1 (July 31, 2014) (hereinafter "FDA CP Response"). For this basic structural reason, an LDT being performed cannot logically be considered commerce between any state or territory.

Even if LDTs are introduced or delivered for introduction into interstate commerce, they are not introduced for "commercial distribution." "Commercial distribution" is defined under 21 C.F.R. § 807.3(b) to mean "any distribution of a device intended for human use which is held or offered for sale," and excludes "[i]nternal or interplant transfer of a device between establishments within the

[189] Charrow Memorandum, *supra* note 35, at 9.

same parent, subsidiary, and/or affiliate company." In a Compliance Policy Guide (CPG), FDA interpreted commercial distribution to require delivery of the device to purchasers or consignees. FDA, CPG § 300.600 ("Commercial Distribution with Regard to Premarket Notification (Section 510(k))") (1978, reissued 1987). Specifically, under this CPG, FDA will consider a device in commercial distribution *without* delivery only if the manufacturer can establish that, among other things, it had accepted or been prepared to accept at least one purchase order before enactment of the MDA "generally *with delivery to occur* immediately or at a promised future date." *Id*. (emphasis added). Thus, FDA has interpreted "commercial distribution" to mean that, at the very least, delivery of the device is anticipated. And notably, a court has upheld this CPG's interpretation of "commercial distribution." *U.S. v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990, 993-95 (W.D. Mich. 1985). In *An Article of Device Consisting of 1,217 Cardboard Boxes*, the court cites CPG 7124.26, which contains identical language regarding delivery of the device, stating such CPG was "the current expression of the [FDA's] interpretation of 'commercial distribution,'" as well as a letter from FDA in which the Agency explained that the requirements for "commercial distribution" would be satisfied if there were "adequate documentation of separate, specially labeled *packaging*, and at least one sale prior to May 28, 1976" (emphasis added). The court then concluded that the explanation in the letter, "together with the agency's compliance policy guide 7124.26, is a reasonable interpretation of the phrase 'commercial distribution'." *Id.* at 994-95.

FDA contends that "commercial distribution" "does *not* require the physical transfer of an object" but only that a device be "on the market." 88 Fed. Reg. 68,021. But that gloss ignores FDA's longstanding interpretation of "commercial distribution," which requires actual or anticipated *delivery*.

For these reasons, LDTs cannot be subject to any FDCA authority that requires introduction or delivery into interstate commerce for commercial distribution. This includes FDA's premarket review requirements under FDCA § 510(k), among many other provisions. This statutory context confirms that LDTs fall outside the scope of "devices." Other provisions of the FDCA also discuss "devices" in ways that only make sense if applied to physical objects. *See, e.g.*, FDCA §§ 513(a)(2)(B) ("labeling" for devices); 514(a)(2)(C) ("labeling for the proper installation, maintenance, operation, and use" of a device); 519(f) (labels that "bear a unique identifier" so that a device can be tracked); 515(c)(1)(C) ("the manufacture, processing, and, when relevant, packing and installation of" a device); 518(b) (requiring a "manufacturer, importer, distributor, or retailer" of a device to "repair," "replace," or "refund the purchase price").

In response to this argument, FDA offers a blithe retort that such tests would then just have to go through the PMA or De Novo pathway. This conclusion—that a device not subject to section 510(k) is independently subject to section 515 or 513(f)(2) of the FDCA—is not supported by the text of the FDCA or FDA's own interpretation of the statute. Rather, submission of a premarket application under section 515 or a De Novo request under section 513(f)(2) *satisfies* the requirement to submit a 510(k) premarket notification, which generally applies to all devices unless subject to a specific exemption.

Specifically, section 510(k) of the FDCA requires a premarket notification prior to introduction of "a device," not a device that is not otherwise subject to premarket approval requirements, De Novo classification requirements, investigational device exemption, or that is otherwise 510(k) exempt. The 510(k) requirement thus applies broadly across all devices, but exemptions from the 510(k) requirements have been added to the FDCA (e.g., for certain class I and

II devices, under section 510(*l*) and (m), and for investigational devices under section 520(g)), or established by FDA through regulation based on its interpretation of the FDCA.

With regard to PMA applications and De Novo classification requests, FDA has interpreted the statute such that a PMA application under section 515 or a De Novo classification request under section 513(f)(2) satisfies the requirement for a premarket notification under section 510(k). In its 1976 proposed rule establishing the Part 807 regulations for premarket notifications, the Agency explained that "[a] premarket notification under § 807.81 is not required for a device for which a premarket application under section 515 of the act, or for which a petition to reclassify from class III to class I or II under section 513(f)(2) of the act, is pending before FDA. For such devices, the other submissions will serve the purpose of a notification under section 510(k) of the act." Proposed Rule, Establishment Registration and Premarket Notification Procedures, 41 Fed. Reg. 37458, 37460 (Sept. 3, 1976). In the final rule establishing such regulations, FDA confirmed this interpretation, explaining that "[i]f a premarket approval application has been submitted, a premarket notification submission would not be required since FDA would already be advised of the intent to market." See Final Rule, Establishment Registration and Premarket Notification Procedures, 42 Fed. Reg. 45250, 42523 (Aug. 23, 1977) (emphasis added).

Moreover, even if FDA were right that LDTs would need to resort to the PMA or De Novo pathway (which it is not), this argument ignores a more fundamental point: it defies logic that Congress would create a system to regulate LDTs where foundational provisions would not apply. By FDA's own estimates, some 80% of LDTs that require premarket review would be subject to the 510(k) premarket notification process. The fact that the principal pathway to market for devices (not to mention other aspects of the FDCA) would be unavailable to LDTs is further evidence that the device regulatory framework was never intended to reach LDTs. This argument also would further undermine FDA's estimate of the costs associated with the Proposed Rule, as the tens of thousands of LDTs that FDA had estimated to be eligible for the 510(k) pathway would be subject to the lengthier, more expensive PMA and De Novo pathways.

D. LDTs are not "held for sale" as required under FDCA Section 301(k).

As an additional basis, FDA has asserted that it may regulate LDTs under Section 301(k) of the FDCA by claiming that LDTs are "held for sale." This argument fails under a commonsense reading of Section 301(k) and applicable case law.

Under 301(k), the following acts are prohibited: "The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, if such act is done while such article is *held for sale* (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded." 21 U.S.C. § 331.

As an initial matter, LDTs are not "article[s]" "held for sale." A physician's test order for an LDT service is satisfied by the laboratory performing in-house testing services and reporting back to the ordering physician the result of that service, not by the laboratory transferring title to and possession of the testing methodology or protocol to the ordering physician as a third-party purchaser.

This view comports with the case law, which extends FDA's jurisdiction to regulate drugs and devices after release by the original manufacturer, but only insofar as such regulated products are

being delivered or transferred to another ultimate consumer. In this regard, *U.S. v. Regenerative Sciences, LLC*, 741 F.3d 1314 (D.C. Cir. 2014), is inapplicable to LDTs. In *Regenerative Sciences*, the court stated that a drug—doxycycline—was adulterated when mixed with cells from patients, and then such drug-cell mixture was held for sale when administered to a patient for treatment. This does not occur with LDTs, however, which by definition are not transferred to anyone, but performed by the developer. Thus, LDTs are not "held for sale." For example, "held for sale" does not include use of a device to facilitate the work of a healthcare professional where that device is not transferred to the patient. *See Shahinian v. Kimberly-Clark Corporation*, No. 14-CV-8390, 2017 WL 11595343 (C.D. Cal. Mar. 7, 2017) (holding surgical gowns were not "held for sale" because they "were bought for the use of [the] hospital staff, the 'ultimate consumer' of the product").

In cases cited by FDA in its Citizens Petition Denial Response and by HHS in the Charrow Memorandum, the regulated drug or device product was delivered or transferred from one party (typically a doctor) *to* an ultimate consumer (typically a patient). *See* Citizen Petition Denial Response from FDA Center for Devices and Radiological Health to ACLA re: Docket No. FDA-2013-P-0667 at 1 (July 31, 2014); *United States v. Cassaro, Inc.*, 443 F.2d 153, 156 (1st Cir. 1971) (citing *Hipolite Egg Co. v. United States*, 220 U.S. 45, 54 (1911), for the proposition that the "held for sale" standard of section 301(k) has long been afforded a liberal reading, encompassing "[a]ll articles, compound or single, not intended for consumption by the producer"); *United States v. Sullivan*, 332 U.S. 689, 697 (1948) (cited for the proposition that section 301(k)'s "held for sale" requirement is "designed … to extend the [FDCA's] coverage to every article that had gone through interstate commerce until it finally reached the ultimate consumer"); *see also United States v. Evers*, 643 F.2d 1043, 1050 (5th Cir. 1981) (summarized by FDA as "stating that physicians holding drugs for use in their practice may be considered to hold them for sale within the meaning of section 301(k) of the FDCA," and where such drugs were delivered to an ultimate consumer, i.e., the patient); *United States v. Diapulse Corp. of Am.*, 514 F.2d 1097, 1098 (2d Cir. 1975) (which FDA quoted for the proposition that "devices, used in the treatment of patients, may properly be considered 'held for sale' within the meaning of the Food, Drug, and Cosmetic Act," and where the device at issue was administered to patient); *United States v. Rhody Dairy, L.L.C.*, 812 F. Supp. 2d 1239 (E.D. Wash. 2011) (holding that drugs are "held for sale" when they are administered); *United States v. Torigan Labs., Inc.*, 577 F. Supp. 1514, 1521 (E.D.N.Y. 1984) ("All articles held for purposes other than personal consumption—whether to be sold or given away—are deemed to be held for sale under the Act."); *Articles of Animal Drug Containing Diethylstilbestrol*, 528 F. Supp. 202, 205 (D. Neb. 1981) ("This Court subscribes the view that an article of drug or device is "held for sale" if it is used for any purpose other than personal consumption."). This does *not* occur with LDTs, or any component of an LDT. Only the test report, which includes *patient-specific information* yielded from performance of an LDT, is transferred back to the ordering physician, and a test report is not a device.

Even if LDTs were "held for sale," section 301(k) only applies while LDTs are "held for sale … after shipment" in interstate commerce. By definition, LDTs are never shipped in interstate commerce. They are performed only within the laboratory in which they are developed. To the extent that the methods for performing LDT services are transferred *anywhere*, it is between laboratories under common ownership and control, which then independently validate such methods. This is not "interstate commerce," as reflected by its exclusion from the definition of "commercial distribution." 21 CFR § 807.3(b).

E. Imposing device law on LDTs would violate the First Amendment.

The FDA's proposal to regulate LDTs—that is, to regulate intangible methodologies, as opposed to the manufacture and sale of physical articles, and the communications between

laboratory directors, clinical consultants, and ordering providers—raises serious constitutional concerns.

The design and execution of LDTs, as well as the communication of test reports to healthcare providers, inherently involves constitutionally protected speech. As explained earlier in these comments, the responsibilities of a high-complexity laboratory director and clinical consultant include ensuring that reports of test results include pertinent information required for interpretation and consulting with the ordering physician (or other health care professional) regarding the appropriateness of the testing ordered and the interpretation of test results. 42 CFR §§ 493.1445 & 439.1457. Accordingly, laboratory directors and clinical consultants are required to share information regarding clinical meaning of analytical test results, including their viewpoints on the meaning of that information for a particular patient. In this way, laboratories act as providers of health care services and are meaningfully different than device (or drug) manufacturers that principally make promotional claims about products and do not provide similar clinical care services.

However, FDA regulation of LDTs as medical devices would necessarily chill this speech. Turning laboratories into medical device manufacturers would restrict speech because device manufacturers and their employees are limited to communicating information that is "on-label," i.e., consistent with the approved or cleared labeling of a device. Accordingly, laboratory directors and clinical consultants would be restricted from sharing any information about the meaning of a test result if FDA has not authorized that speech.

To the extent that FDA would regulate speech about the interpretation of test reports based on its content (for example, limiting test report statements, or statements made during a clinical consultation, regarding the effect of a patient's genetic makeup on drug response until FDA has reviewed or approved such statements) or viewpoint (for example, limiting expression in a test report, or during a clinical consultation, of a view that is a matter of scientific debate, such as the relative importance of a particular biomarker to diagnosing a particular disease), strict scrutiny, or at a minimum heightened scrutiny, applies. *See NIFLA v. Becerra*, 138 S. Ct. 2361, 2371–75 (2018) (speech by professionals is not exempt from the rule that content-based regulations of speech are subject to strict scrutiny); *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 565 (2011) (heightened scrutiny applied to regulation of speech in aid of pharmaceutical marketing). Strict scrutiny properly applies to such speech because it does not propose a commercial transaction and is not an advertisement or otherwise clearly commercial. *See Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 66–67 (1983).

Even under the less stringent standards applicable to commercial speech, FDA would be hard-pressed to justify its restrictions because FDA could achieve its stated goals through alternative, less-intrusive means. Under *Central Hudson Gas Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557 (1980), a three-part test applies to determine whether a restriction on lawful and not misleading commercial speech is permissible: (1) the asserted governmental interest must be substantial, (2) the regulation must be in proportion to that interest, and (3) the regulation must be designed carefully to achieve the government's goal. *Central Hudson*, 447 U.S. at 564. Here, although FDA asserts a general concern about unreliable LDTs, it does not identify a particular substantial governmental interest in controlling what non-misleading information may be communicated in a test report. *See Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 197, 225–27 (S.D.N.Y. 2015). The FDA is also unlikely to be able to show that "the regulatory technique" proposed (that is, the application of speech-limiting "device" regulations to LDTs) is in proportion to whatever substantial "interest" it may have. *Central Hudson*, 447 U.S. at 564. The FDA has an interest in ensuring that *misleading* information is not communicated in a test report, but requiring burdensome FDA approval or clearance of *any* change in reporting suppresses far more expression than would serve the FDA's

interest. *See id.* at 565. Finally, in this dynamic, cutting-edge industry, there is a serious risk that regulating LDTs as devices would undermine the goal of ensuring that appropriate information is conveyed to providers in connection with the tests they order. As the CLIA regime recognizes, clinical laboratories should be able to provide pertinent updates on testing information as soon as it is available. FDA regulation of LDTs as devices would prevent that expression.

F. FDA regulation would interfere with the practice of medicine.

Laboratories employ licensed pathologists, genetic and clinical counselors, and other licensed medical professionals, and these professionals are an integral part of patients' medical teams. As explained in section II.B, above, the laboratory director is responsible for ensuring that selected test methodologies "have the capability of providing the quality of results required for patient care," "reports of test results include pertinent information required for interpretation," and "consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific conditions." 42 CFR § 493.1445(e)(3)(i), (e)(8) - (e)(9). The laboratory also must be staffed with someone who qualifies as a clinical consultant, who is expressly responsible for "provid[ing] consultation regarding the appropriateness of the testing ordered and interpretation of test results." *Id.* § 493.1457.

In practice, many clinical laboratories have entire medical teams dedicated to these functions, which include the application of medical judgment when interpreting test results, annotating test reports, and consulting with the patient's care team. Regulating laboratories as device manufacturers would restrict the ability of these medical professionals to fully express their medical judgment, which may include the practice of medicine as recognized by law in some states. *See, e.g.*, Utah Code Ann. §§ 58-67-102(19)(a) ("Practice of medicine" means "(i) to diagnose ... by any means or instrumentality") & 58-67-102(12)(a) ("Diagnose" means "to examine in any manner another person, parts of a person's body, substances, fluids, or materials excreted, taken, or removed form a person's body, or produced by a person's body, to determine the source, nature, kind, or extent of a disease or other physical or mental condition"). In particular, the attendant restrictions on providing interpretations or off-label information would interfere with their ability to appropriately consult with ordering physicians. FDA is prohibited, however, from regulating the practice of medicine under section 1006 of the FDCA. *See also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001) (FDA's "mission [is] to regulate ... without directly interfering with the practice of medicine.")

G. The NPRM Fails to Comply with Section 553(b) of the Administrative Procedure Act.

As amended by the Providing Accountability through Transparency Act of 2023, Section 553(b) of the Administrative Procedure Act requires that a Notice of Proposed Rulemaking include "the Internet address of a summary of not more than 100 words in length of the proposed rule, in plain language, that shall be posted on the Internet website under section 206(d) of the E-Government Act of 2002 (44 U.S.C. 3501 note) (commonly known as regulations.gov)." 5 U.S.C. § 553(b)(4). The NPRM fails to comply with this requirement, as it does not include the Internet address at which such a summary may be found, nor does the rulemaking docket for the Proposed Rule at regulations.gov include any summary of the rule, much less "summary of not more than 100 words in length of the proposed rule, in plain language."

That omission undermines the ability of stakeholders—particularly smaller laboratories and their employees—to understand FDA's proposal and participate meaningfully in the public comment process. Congress determined that a "plain language" summary is essential to providing

"[a]ccountability" and "[t]ransparency" in rulemaking proceedings, Pub. L. No. 118-9, § 1, and thus mandated that every "notice of proposed rulemaking … *shall* include" the required summary, 5 U.S.C. § 553(b)(4) (emphasis added). FDA accordingly must publish a concise summary of its proposal, reissue the Notice of Proposed Rulemaking with the mandatory Internet address included, and then restart this proceeding with a new public comment period.

VII. The Agency Could Revise the Rule to Reduce, but not Eliminate, the Net Negative Impact of the Rule to Public Health.

As explained in these comments, ACLA believes that FDA should not finalize the Proposed Rule. As a matter of law, the Proposed Rule exceeds FDA's authority and raises significant constitutional issues. Moreover, even if FDA had authority to move forward (which it does not), the Proposed Rule should be abandoned because it is bad policy. However, the Proposed Rule seeks comment on FDA proposals that FDA suggests could lessen the harm caused by the Proposed Rule. If FDA nonetheless decides to ignore the deficiencies set forth in these comments and proceeds in finalizing the Proposed Rule, it could adopt certain approaches to lessen the harm caused by the Proposed Rule. However, we emphasize that none of these, individually or collectively, would cure the legal or policy deficiencies identified throughout these comments, nor would they completely eliminate the net harm of the Proposed Rule such that its benefits would outweigh its costs. Nothing in the following comments should be regarded as ACLA conceding that FDA has a legal or public policy basis to proceed with this rulemaking.

A. Grandfathering for existing tests.

To reduce but not eliminate the net harm of the rule, all LDTs that are first made available prior to publication of the final rule could be subject to ongoing enforcement discretion and not be expected to comply with premarket submission requirements or quality system requirements related to design controls. This mitigation would reduce the costs for both laboratories and FDA related to the backward-looking exercise of re-validating and submitting applications for existing tests. Accordingly, it would also mitigate the harms to patients from important tests being culled from existing test menus and would lessen (but not eliminate) the need to divert existing resources currently focused on innovation and clinical testing, thus lessening the net negative impact of the rule to innovation and patient access to important tests.

Failing to grandfather existing tests from at least these portions of FDA regulation also would improperly disregard the legitimate reliance interests of clinical laboratories that offer these LDTs, as well as the interests of the patients who would otherwise benefit from tests suddenly rendered uneconomical. *See DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913-15 (2020) (failing to consider reliance interests of DACA recipients, and weigh those interests against competing concerns, was arbitrary and capricious). Those reliance interests are substantial, given FDA's decades-long policy of generally not enforcing device requirements with respect to LDTs and the countless business decisions affecting the landscape of the U.S. health care system that have been made against the backdrop of that policy.

Importantly, FDA's proposed exemptions for "1976-type" LDTs are neither adequate nor sensible to lessen the high costs to laboratories and patients in the Proposed Rule. The exemption for "1976-type" LDTs is limited only to those tests that use "manual techniques (without automation)." However, these types of tests are few and far between. Even simple laboratory tests that existed in 1976 have since been updated to leverage automated systems, such as automatic pipetting, that improve the accuracy, consistency, and quality of such tests. For example, while a

cytogenetics test *can* be performed without automated instrumentation, it is commonly performed using an automated metaphase finder to locate cells for karyotype and analysis. As another example, differential cell counts used to be performed manually by a laboratory technician performing a manual blood smear and counting cells; but now, automation lines draw the blood, prep the smear, and count the cells, with only certain abnormal findings triggering a manual review by a technician or pathologist. This extremely narrow exemption, therefore, would only encourage less accurate, less consistent, and lower quality methods of testing. Instead, FDA could further mitigate the net negative impact of the rule by exempting all LDTs that are offered prior to finalization of the rule, regardless of complexity or risk-level.

It would mitigate the net negative impact of the rule to a lesser degree to grandfather only those tests that have been previously approved by New York State—regardless of risk classification. Such tests have been evaluated for their analytical and clinical validity by a third party that FDA itself previously has relied upon for third-party reviews. However, we note that grandfathering tests approved by the state of New York would be inadequate to completely alleviate laboratories from having to cull certain tests from their menus and to prevent FDA from being overwhelmed by marketing submissions at years 3.5 and 4 of the phaseout period. This is because such a policy would not extend to laboratories outside of New York that do not offer tests nationally, e.g., local, specialty laboratories, and New York does not review and approve *all* LDTs. For example, New York does not review and approve LDTs for multi-analytic immunohistochemistry stains, which it considers to be performed by "standard methods."[190]

B. Extended implementation timeline.

The implementation timeline could be extended for all tests to reduce, but not eliminate, the net harm of the rule. Four years to phase in an ill-fitting regulatory regime is hardly appropriate given the significant amount of work that would be needed to bring activities into compliance. Even in 2014, when FDA proposed through draft guidance to phase-in device regulation of LDTs, the Agency proposed a 9-year transition period.[191] In the VALID Act, a bill for which FDA gave substantial input and which was re-introduced as recently as March 2023, a transition period of up to 10 years was available for certain tests in addition to grandfathering of all LDTs available at the time of enactment.[192] Extending the implementation timeline would enable laboratories to stretch their existing resources more efficiently compared to the implementation timeline as proposed, such that fewer personnel would need to be completely diverted away from their existing innovation/testing activities to focus on backward-looking re-validations and establishing FDA-compliant quality and postmarket systems. It would also mean that fewer new personnel would need to be hired, and, ultimately, fewer existing tests may need to be culled from test menus due to

---

[190] *Test Approval*, DEP'T OF HEALTH, WADSWORTH CENTER, https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval (last visited Nov. 15, 2023).

[191] FDA, DRAFT GUIDANCE: FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOPED TESTS 26 (2014), https://www.fda.gov/media/89841/download.

[192] Press Release, Office of Congresswoman Diana Degette, *Lawmakers move to reform diagnostic testing in U.S., FDA says legislation is a 'top priority' for the agency* (Mar. 29, 2023), https://degette.house.gov/media-center/press-releases/lawmakers-move-reform-diagnostic-testing-us. Text of the bill is available here: https://degette.house.gov/sites/evo-subsites/degette.house.gov/files/evo-media-document/118-valid-act.pdf.

competing demands for limited resources that make obtaining clearance or approval for all existing tests impossible. Accordingly, this would reduce, but not eliminate, the negative impact of the rule to innovation and access to testing. Finalizing the Proposed Rule without extending the transition period would harm the reliance interests of clinical laboratories engendered by FDA's decades-long policy of generally not enforcing device requirements with respect to LDTs. *See DHS v. Regents of the Univ. of Cal.*, 140 S. Ct. 1891, 1913-15 (2020) (where agency is "not writing on a blank slate," it must consider reliance interests).

Additionally, FDA could further extend the implementation timeline for LDTs approved by New York State that are introduced after publication of the final rule to reduce, but not eliminate, the net harm of the rule. As discussed above, New York State evaluates the analytical and clinical validity of LDTs, and extending the transition period for these tests would be consistent with the recognition that they have already been evaluated by a third party for analytical and clinical validity. In addition to the reduced harm to laboratories and patients that would accrue from a longer implementation timeline, this would also lessen the burden to FDA of reviewing thousands of submissions submitted all at once when submissions become due. Instead, FDA could focus on those tests for which there has been no independent review and would still receive at a later date premarket submissions for tests that have received New York State approval. This was the approach adopted in VALID, where tests approved by New York State under molecular specialties would have received an additional 5 years for transition, and all other tests approved by New York State would have received an additional 2 years.

ACLA disagrees with all discriminatory applications of LDT regulation based on the type of entity offering the LDT, including but not limited to the proposal in the Proposed Rule to extend the implementation timeline only for small laboratories with revenues below a certain threshold. There is no public health basis for granting only these small laboratories a longer transition period, and doing so would be completely inconsistent with one of FDA's underlying arguments in the Proposed Rule – that the same regulatory requirements should apply to the same activities, regardless of where or by whom they are performed.

C. New York State and MolDX programs.

FDA could recognize approvals by New York State and coverage decisions by MolDX as clearances and approvals of LDTs for purposes of device regulation to reduce, but not eliminate, the net harm of the rule. As detailed above, both of these programs review LDTs for their analytical and clinical validity based on detailed technical submissions. Accordingly, FDA could reduce, but not eliminate, net harm from the rule by recognizing their decisions as satisfying the FDA requirement for clearance or approval by exercising enforcement discretion for tests that have gone through such programs, or, at minimum, structure an expedited approval/clearance pathway that would alleviate the burden of FDA re-review of such tests. Likewise, with respect to LDT clinical trial assays that New York State permits to be used for clinical management without prior approval, FDA could reduce the net harm of the rule by continuing enforcement discretion with respect to such clinical trial assays. Without leveraging these programs, by FDA's own estimate, the Agency would face an annual increase in premarket submissions of 500% for PMA Submissions, 500% for De Novos, and 80% for 510(k)s. Leveraging these programs would reduce, but not eliminate, the burden on both laboratories and FDA associated with implementation of the Proposed Rule.

D. Flexible modifications policy.

To lessen the burden on laboratories and FDA associated with premarket submissions for modifications to cleared and approved tests as discussed above, FDA could develop a flexible approach that enables laboratories to modify cleared and approved tests without premarket review.

For example, the VALID Act would have allowed CLIA-certified high-complexity laboratories or the marketing authorization holder (if not a high-complexity laboratory) to make certain modifications to an approved test without seeking independent premarket review. Modifications exempt from premarket review would have included modifications that do not (a) significantly change the indications for use, except for some changes to specimen type; (b) cause the test to no longer comply with mitigating measures or restrictions (conceptually similar, but not the same, as special controls); (c) significantly change performance claims or significantly and adversely change performance; or (d) adversely change the safety for individuals who come in contact with the test. Importantly, the VALID Act made clear that modifications to extend specimen stability would have been exempt as long as they met such requirements. And FDA still has a flexible policy for modifications by high-complexity laboratories to EUA-authorized COVID-19 tests. Under the current COVID-19 Testing Guidance, a high-complexity CLIA-certified laboratory can modify an EUA-authorized test, including one for which the laboratory does not hold the EUA, if the modifications do not change the indications for use set forth in the EUA and do not change the analyte specific reagents.[193]

A flexible policy for such modifications, established through complementary amendments to the FDCA and CLIA regulations or through continued FDA enforcement discretion, could reduce loss of availability of important tests that are modified to enhance performance and improve patient access. Specifically, FDA, CMS, and CDC could reduce but not eliminate the net harm of the rule by coordinating on complementary regulations to distinguish between modifications to cleared or approved IVDs, which would remain subject to CLIA exclusively, and novel LDTs for which FDA might require premarket review. To maximize harm reduction, this flexible modifications policy would need to extend to grandfathered tests, as well, because failure to do so would quickly render any grandfathering policy obsolete as modifications are routinely made to improve performance and adjust to changing circumstances.

The VALID Act also proposed a Technology Certification Program, under which test developers that received a technology certification order could introduce non-high-risk tests without individual tests undergoing premarket review. To be eligible to participate in the program, the developer had to have demonstrated expertise in a particular technology and a commitment to quality systems. In addition to reducing the administrative burden for non-high-risk tests, the program necessarily would have accommodated modifications to such tests. To reduce the net harm from the Proposed Rule, FDA could consider whether it could establish a similar program (as it did with the Digital Health Precertification Program) to facilitate a more flexible policy toward modifications and the introduction of new tests. To the extent that FDA believes that such a program would not be appropriate, or if FDA believes that it lacks legal authority to implement such a program, those positions should be considered and explained.

---

[193] FDA, *Policy for Coronavirus Disease-2019 Tests (Revised)** at 12 (Jan. 12, 2023).

E. Enforcement discretion for low-volume tests.

FDA could continue to exercise enforcement discretion for low-volume tests, at least for the requirements for premarket review, to reduce but not eliminate the net harm of the rule. As detailed earlier, many LDTs are not used at volumes that justify the cost of a premarket submission (including PMAs, De Novo or even 510(k)). Although some of these tests are for rare diseases that would fit within the Humanitarian Device Exemption (HDE) pathway, many would not, given the extremely low HDE ceiling for patient groups that can be served by a diagnostic test under the HDE program. Other low volume tests would be used very infrequently, significantly less than the thresholds contemplated by the HDE program.

Even for those tests that would satisfy the thresholds for an HDE, the requirements and burdens associated with obtaining an HDE are not trivial, and in most cases the costs would not justify development and approval of the tests. Moreover, the HDE prohibits test developers from commercializing their assay except under narrow conditions. Given the public health contribution of these tests – and the fact that many would be abandoned if FDA proceeds with the Proposed Rule – FDA could exercise enforcement discretion from premarket requirements for low-volume LDTs to reduce the net harm of the rule. To do this, FDA could define a "low volume" test and fully explain the basis for any chosen volume limit for this category through notice and comment rulemaking.

F. Classification panels.

FDA could establish classification panels for currently available LDTs, as it did for medical devices when the MDA was enacted, to reduce the net harm of the rule. By FDA's estimates, there are 80,400 LDTs currently available that would require premarket review. Even if these tests are grandfathered, unless there is a sensible modifications policy, FDA would quickly be flooded with premarket submissions for LDTs. But clinical laboratories are not experienced at selecting predicate devices, and even if they were, there are not suitable predicate devices for all of their tests, which would force them through the more burdensome and expensive PMA or De Novo pathway. Even low-risk novel tests would have to go through the De Novo pathway. To streamline premarket submissions for LDTs, FDA could issue an RFI regarding available LDTs and classify tests so that laboratories would have more clarity on the appropriate premarket submission pathway for their new and modified tests (and existing tests, if not grandfathered).

G. CLIA regulation.

FDA could consult with CMS and CDC on an alternative approach whereby CLIA regulations are updated with appropriate additional requirements for validation of LDTs, including modifications to cleared and approved IVDs and novel LDTs. If FDA rejects this approach, it must provide a reasoned basis for doing so. A mere conclusory statement that the Proposed Rule is complementary to the CLIA regulations is not only insufficient; it is patently wrong. CLIA regulations expressly acknowledge that laboratories may "modif[y] an FDA-cleared or approved test system, or introduce a test system not subject to FDA clearance or approval,"[194] and the Proposed Rule creates a conflict between FDA's regulations and CLIA's longstanding and relied-upon regulations. CLIA also requires compliance with its own quality system regulations, requires laboratories to be inspected, and imposes fees on laboratories.

---

[194] 42 CFR § 493.1253(b)(2).

H. Request for information (RFI).

As explained earlier in these comments, FDA made no attempt to collect information about the number of high-complexity CLIA laboratories or LDTs currently being offered that would be affected by the Proposed Rule, despite the Agency having the tools to do so. For example, FDA could have coordinated with other HHS agencies, CMS and CDC, to collect information from CLIA-certified laboratories regarding the number of laboratories that are high-complexity laboratories and the number of LDTs offered by each such laboratory. FDA also could have issued an RFI seeking information regarding the number of high-complexity clinical laboratories and the number and type of LDTs currently being offered.

Failing to obtain this information prior to finalizing the Proposed Rule would be irresponsible and undoubtedly maximize the harm from the rule. Accordingly, FDA could potentially mitigate, but not eliminate, the harm from this proposed rule by first issuing an RFI for information about high-complexity clinical laboratories that would be affected and the number and type of LDTs currently available, thereby increasing the likelihood that any finalized policy is informed by accurate data.

I. Equal treatment of LDT developers.

ACLA strongly believes there is no reasoned basis for exempting particular laboratories from any FDA policy regarding LDTs or otherwise singling out any category of LDT developer for disparate treatment. FDA should not go forward with the Proposed Rule with special, different rules for small laboratories, large laboratories, academic medical centers (AMCs), laboratories in particular states or locations, or other categories of test developers.

FDA requested comments specifically on whether a different policy should apply for LDTs offered by AMCs. ACLA appreciates the important role of AMCs in the health care delivery system and the scientific and clinical expertise developed within AMCs, and we recognize their contributions to clinical and medical research. However, as FDA notes in the Proposed Rule, there is no established definition of an AMC laboratory, and defining any other developer-based exemption would face similar challenges. Further, differences in expertise in test development and the quality of testing at AMCs and commercial laboratories are not supported by evidence. Additionally, there is no meaningful difference between the tests offered by AMCs and commercial laboratories. The test menus offered by large AMCs and commercial laboratories are similar.[195] In that regard, both AMCs and commercial laboratories are engaged in routine testing and in supporting care for patients with rare diseases and unique conditions. Importantly, establishing an exemption for AMCs could create negative health disparities for populations without access to an AMC.

In sum, there is no reasoned basis for treating particular test developers, including AMCs, differently than commercial laboratories, and doing so would be arbitrary and capricious in violation of the Administrative Procedure Act (APA). *See Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997) ("The disparate treatment of functionally indistinguishable products is the essence

---

[195] *See, e.g.*, UCSF Health Clinical Laboratories, *UCSF Health Clinical Laboratories Test Directory*, https://www.testmenu.com/UCSFClinLab (last visited Nov. 11, 2023); Stanford Medicine, *Stanford Medicine Test Directory*, https://stanfordlab.com/content/stanfordlab/en/test-directory/search-results.html#&page=1 (last visited Nov. 11, 2023); NYU Langone Health, *NYU Langone Health Clinical Laboratories Test Directory*, https://www.testmenu.com/nyumc (last visited Nov. 11, 2023).

of the meaning of arbitrary and capricious.") (citations omitted). Indeed, failure to treat similarly situated parties similarly would be regarded as arbitrary and capricious under the APA and would provide yet another basis for a legal challenge to FDA's regulation of LDTs. *Grayscale Investments v. SEC*, 82 F. 4th 1239 (D.C. Cir. 2023); *Nasdaq Stock Market LLC v. SEC*, 38 F.4th 1126 (D.C. Cir. 2022)

CONCLUSION

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

Exhibit 1: Professor Chris Carrigan, Global Economics Group, Review of the Food and Drug Administration's Preliminary Regulatory Impact Analysis for its Medical Devices; Laboratory Developed Tests Proposed Rule

Review of the Food and Drug Administration's Preliminary Regulatory Impact Analysis for its Medical Devices; Laboratory Developed Tests Proposed Rule

Christopher Carrigan[1]

December 4, 2023

[1] I am Associate Professor of Public Policy and Public Administration at George Washington University's Trachtenberg School of Public Policy and Public Administration and a Co-Director of the GW Regulatory Studies Center.

Executive Summary:

- In October 2023, the Food and Drug Administration's ("FDA") Office of Economics and Analysis ("OEA") released a preliminary Regulatory Impact Analysis ("RIA") to accompany FDA's proposed rule, "Medical Devices; Laboratory Developed Tests" ("Proposed Rule") as required by Executive Orders 12866 and 14094 for all rules deemed by the Office of Information and Regulatory Affairs ("OIRA") to be 3(f)1 significant.[2]

- OEA's RIA fails, on several dimensions, to adhere to the standards described in the academic literature as well as the Office of Management and Budget's ("OMB") Circular A-4, which provides guidance to agencies in producing RIAs that fulfill the requirements of the executive orders.[3] These issues result in an RIA that: 1) significantly understates costs by failing to quantify a key ancillary effect; 2) substantially inflates benefits by misusing benefit transfer methods; 3) provides limited ability to evaluate reasonable alternative regulatory approaches; and 4) offers minimal discussion of the distributional effects, including those on marginalized and underserved communities.

- In OEA's analysis, the primary benefits originate in the Proposed Rule's perceived role in reducing misdiagnoses from what OEA refers to as "problematic" laboratory developed tests ("LDTs"), which account for over 98 percent of the total benefits described in the RIA. Similarly concentrated, OEA's estimates of the costs are largely derived from one-time and ongoing reporting, registration, and approval process requirements for LDTs. Of these costs, close to 100 percent of one-time costs and roughly 89 percent of recurring compliance costs originate in premarket approval applications, 510(k) notifications, and De Novo requirements that would apply to LDTs.[4]

- The compliance costs OEA estimates that the Proposed Rule would impose on laboratories offering LDTs are substantial. Based on data provided in the RIA, laboratories would be required to use nearly three and a half years of their gross profits from LDTs just to be able to cover the one-time compliance costs introduced by the Proposed Rule. And this estimate does not account for the fact that gross profit excludes categories of costs that would substantially reduce what is available to laboratories to pay for these newly introduced compliance costs nor does it incorporate the actual fees

[2] Laboratory Developed Tests Proposed Rule Regulatory Impact Analysis, (Oct. 3, 2023), available at fda.gov/about-fda/economic-impact-analyses-fda-regulations/laboratory-developed-tests-regulatory-impact-analysis-proposed-rule. Subsequently, this RIA is referred to as "Proposed Rule RIA." Medical Devices; Laboratory Developed Tests Proposed Rule, 88 FR 68006 (Oct. 3, 2023); Executive Order 12866, Regulatory Planning and Review, 58 FR 51735 (Oct. 4, 1993); and Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023). All referenced material cited should be considered incorporated into this comment. I would be pleased to provide copies of any cited references (subject to copyright or paywall limitations).

[3] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003). OMB released an updated version of Circular A-4 on November 9, 2023. However, the previous version applies to RIAs for proposed, interim final, and direct final rules received by OIRA before March 1, 2024, and for final rules received before January 1, 2025. Therefore, OMB's 2003 version of the Circular applies to the Proposed Rule.

[4] Proposed Rule RIA, at pp. 53-4, 85.

laboratories would pay FDA to accompany submissions, which are considered transfers in the RIA.

- In addition to compliance costs, Circular A-4 explicitly requires agencies to consider ancillary costs in their RIAs.[5] Further, OEA acknowledges that the significant compliance costs they estimate have the potential to force laboratories to discontinue offering certain LDTs. However, they argue they are unable to estimate these ancillary costs due to lack of data. Still, using data already presented in the RIA coupled with the approach that OEA indicates it would employ to quantify this effect reveals that the Proposed Rule would put roughly 90 percent or more of existing LDTs at risk of no longer being offered. And this assumes that all existing LDTs requiring approval would be eligible for the most cost-effective pathway, which necessitates a predicate device so is not likely to be an option for many of them, something OEA acknowledges in their analysis.

- Utilizing the same monetary estimates OEA employs in the RIA to value the benefits of extending lives reveals that the associated annual costs from lost LDTs in shortening lives would likely be double OEA's estimate of the Proposed Rule's annual benefits. Moreover, these recurring health costs associated with at-risk LDTs leaving the market would easily surpass, in one year, any savings associated with a reduction in the already sizable one-time approval costs because at-risk LDTs would leave the market rather than be subjected to FDA's premarket approval process.

- Much like the RIA substantially understates the Proposed Rule's costs, it also significantly overstates its benefits. By extrapolating benefits from only one disputed study and misapplying the results of that study to develop an estimate of lives extended by substituting FDA-approved tests for so-called "problematic" LDTs, OEA fails to adhere to Circular A-4 principles for applying benefit transfer.[6] Even the study OEA cites indicates it is inappropriate to extrapolate to a broader set of LDTs from just their small-sample study. Further, utilizing more recent research that corrects for the errors of the flawed study on which OEA relies suggests the annual benefits are roughly one-third of what the RIA estimates.

- This does not even account for the fact that OEA's specific approach to measuring benefits assumes that all misdiagnoses from "problematic" LDTs will be eliminated by shifting to FDA-approved tests, an assumption OEA contradicts in the RIA and is not supported in the medical literature. Employing a simpler approach that avoids this issue and allows the analysis to incorporate a larger number of medical studies examining the relative level of accuracy of LDTs and FDA-approved tests, as Circular A-4 recommends, benefits are a quarter to one-half what the RIA estimates, consistent with results from correcting OEA's approach directly.

[5] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 26.
[6] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at pp. 24-6.

- Consideration of alternatives is especially important for the Proposed Rule because its considerable costs – both in complying with the rule and associated health effects from at-risk LDTs – coupled with much smaller benefits suggest that alternative, less draconian approaches may be preferred. It is notable that the current framework utilized by the Centers for Medicare & Medicaid Services ("CMS") under the Clinical Laboratory Improvement Amendments ("CLIA") to oversee laboratories that develop LDTs incorporates elements of an approach labeled management-based regulation in the academic literature, which is appropriately used in US regulatory contexts similar to the environment in which LDTs are developed and deployed, including by FDA itself.[7]

- In its analysis of alternatives, OEA also briefly describes but fails to quantify net benefits for two other regulatory approaches that would still phase out the general enforcement discretion approach for LDT registration, listing, and adverse event reporting but would not subject existing LDTs to premarket review requirements. The second would also continue general enforcement discretion for LDTs receiving approval from the New York State Clinical Laboratory Evaluation Program ("CLEP"), including those developed after the final rule.[8] Given the relevant market failure is asymmetric information, these options have the attractive quality that they feature information remedies, which Circular A-4 recommends in these types of cases.[9] Because many of the necessary elements are already available, presenting a quantitative analysis of the benefits and costs of these alternatives should not be overly burdensome for OEA. The primary source of uncertainty would be in estimating the proportion of new LDTs that would opt for approval under New York's CLEP rather than FDA's processes, which could be dealt with using relative cost data or reasonable assumptions.

- Finally, Circular A-4 directs agencies developing RIAs to analyze the distributional effects of the rule.[10] The impact of the Proposed Rule on LDT prices receives very limited attention in OEA's RIA. Yet, for LDTs that can remain in the market, providers will be forced to raise prices to manage the burden of significant additional compliance costs. As prices rise for health care services, including diagnostic tests, because of the Proposed Rule, quantity demanded will decrease, and more so for those with higher price elasticities, including low-income as well as underinsured and uninsured individuals. Given that the latter group especially is disproportionately concentrated among minorities, they will bear more of the burden in increased mortality rates as a result. Given the Biden administration's emphasis on broadening participation of traditionally underserved communities in the regulatory process, it would seem OEA must do much more to evaluate the distributional effects of the Proposed Rule than they currently do to fulfill adequately their obligations under Circular A-4.[11]

---

[7] See, e.g., Coglianese, Cary, and David Lazer. "Management-Based Regulation: Prescribing Private Management to Achieve Public Goals." *Law and Society Review* (2003) 37(4): 691-730.
[8] Proposed Rule RIA, at pp. 100-3.
[9] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 9.
[10] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p 14.
[11] Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023).

- Resolving these issues – including quantifying ancillary costs, appropriately applying benefit transfer, quantifying the effects of meaningful alternatives, and considering the distributional effects of LDT price changes – will result in an RIA that adheres to basic principles outlined in Circular A-4 and reveals that, in fact, the quantified costs substantially exceed the quantified benefits of the Proposed Rule. Perhaps even more importantly, addressing these issues can allow OEA's RIA to fulfill its role in providing a transparent view of the likely effects of the Proposed Rule such that stakeholders and the public more generally can more accurately assess whether its benefits justify its costs.

I. Background 7
A. Analysis Requirements for Economically Significant Rules 8
B. Discussion of the Central Components of OEA's RIA 8
II. The RIA's Estimate of the Proposed Rule's Costs 9
A. Examining LDTs at Risk of Exiting the Market 9
B. Comparing Social Costs of At-Risk LDTs to the Proposed Rule's Benefits 12
C. Using Industry Evidence to Substantiate Estimated Costs from Lost LDTs 14
III. The RIA's Estimate of the Proposed Rule's Benefits 15
A. Evaluating the Appropriateness of OEA's Benefit Transfer Approach 16
B. Assessing the Benefits Associated with Shifting to FDA-Approved Tests 19
IV. Other Important Considerations in Preparing the RIA 21
A. Considering Reasonable Alternatives to FDA's Preferred Approach 21
B. Separately Evaluating the Distributional Effects of the Proposed Rule 24
V. Conclusion 26

I. Background

I was engaged by the American Clinical Laboratory Association ("ACLA") to assess OEA's preliminary RIA accompanying FDA's Medical Devices; Laboratory Developed Tests Proposed Rule.[12]

I am Associate Professor of Public Policy and Public Administration at George Washington University as well as a Co-Director of the GW Regulatory Studies Center. My expertise as an academic centers on regulatory policymaking, and my research has examined a variety of topics relevant for evaluating the application of economic analysis in specific regulatory contexts, including roles that analysis plays in agency regulatory decision-making, design of informative RIAs, factors that influence rule timing and durability, and the variety of approaches that regulatory agencies employ to achieve regulatory goals. In addition to publications in leading academic journals and edited volumes focused on regulation, public policy and administration, political science, and economics, I am the author of the Cambridge University Press book, *Structured to Fail? Regulatory Performance under Competing Mandates*, and a co-editor of the University of Pennsylvania Press volume, *Does Regulation Kill Jobs?* I hold a PhD in public policy from Harvard University, an MBA from the University of Chicago, and a BA in economics from Davidson College.

In conducting my examination, I reviewed the analysis prepared by OEA from the perspective of the procedures that FDA, or any executive branch regulatory agency, is to follow when developing an RIA to support a proposed rule. In performing this analysis, I was supported by staff of Global Economics Group, who worked under my direction.

My overarching conclusion is that the RIA does not fulfill the standards for economic analysis that federal agencies are to follow in several key areas. The discussion of the Proposed Rule's potential costs focuses primarily on compliance costs that laboratories will face in complying with the Proposed Rule if it is finalized while largely ignoring and failing to quantify, with available data, the ancillary and substantial negative health-related and mortality costs that will result from imposing a new regulatory framework on LDT providers. Additionally, the RIA makes inappropriate use of a benefit transfer approach to extrapolate benefits from only one disputed study and misapplies the results of that study to develop an estimate that significantly inflates the Proposed Rule's benefits.

These concerns, coupled with limited quantitative consideration of reasonable alternatives and key distributional effects, lead to an RIA that significantly overstates benefits, dramatically understates costs, provides limited ability to evaluate alternative approaches relative to the Proposed Rule, and obscures significant negative distributional effects on uninsured and traditionally underserved communities. Resolving these issues will result in an RIA that adheres to basic principles outlined in OMB guidance and reveals that, in fact, the quantified costs substantially exceed the benefits of the Proposed Rule. Perhaps even more importantly,

[12] Proposed Rule RIA. Medical Devices; Laboratory Developed Tests Proposed Rule, 88 FR 68006 (Oct. 3, 2023).

addressing these issues can allow OEA's RIA to fulfill its role in providing a transparent assessment of the likely effects of FDA's Proposed Rule such that stakeholders and the public more generally can more accurately assess whether its benefits justify its costs.

A. Analysis Requirements for Economically Significant Rules

OMB's Circular A-4 provides a set of principles to guide executive branch agencies in their preparation of RIAs, which are required by Executive Orders 12866 and 14094 for all rules deemed by OIRA to be 3(f)1 significant in order to demonstrate that the benefits of that rule justify its costs.[13] OIRA determined that FDA's Proposed Rule is 3(f)1 significant.[14]

These principles, as well as best practices established in the academic literature, offer clear guidance on the elements to be included in an RIA that fulfills the requirements of the executive orders.[15] These elements include:

1) a discussion of the need for the rule, based on the problem the rule seeks to remedy;
2) consideration of not just of the rule's direct benefits and costs but also the ancillary benefits and indirect costs or countervailing risks;
3) careful consideration of how studies are selected if benefit transfer methods are used, recognizing that other approaches to valuing benefits are generally preferred;
4) consideration of reasonable alternatives to the approach advocated by the agency; and
5) examination of the distributional effects of the rule in a separate analysis.

B. Discussion of the Central Components of OEA's RIA

The primary source of benefits in OEA's preliminary RIA derives from the Proposed Rule's role in reducing misdiagnoses from what they refer to as "problematic IVDs offered as LDTs."[16] OEA suggests that these annual benefits, which they estimate total $26.4 billion or $39.6 billion (depending on the choice of discount rate), will result from improved health outcomes in the form of reduced baseline mortality risk.[17] These benefits originate from an expected reduction in misdiagnoses from in-vitro diagnostic products ("IVDs") offered as LDTs and represent over 98 percent of the total benefits presented in the RIA.[18]

OEA's estimates of the costs of the Proposed Rule are similarly concentrated, with the majority derived from focusing on the compliance costs that would be imposed on laboratories associated with one-time and ongoing reporting, registration, and approval process requirements.

---

[13] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003); Executive Order 12866, Regulatory Planning and Review, 58 FR 51735 (Oct. 4, 1993); and Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023).
[14] Medical Devices; Laboratory Developed Tests Proposed Rule, 88 FR 68027 (Oct. 3, 2023).
[15] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003); Executive Order 12866, Regulatory Planning and Review, 58 FR 51735 (Oct. 4, 1993); Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023); and see, e.g., Dudley, Susan, et al. "Consumer's Guide to Regulatory Impact Analysis: Ten Tips for Being an Informed Policymaker." *Society for Benefit-Cost Analysis* (2017) 8(2): 187-204.
[16] Proposed Rule RIA, at p. 1.
[17] Proposed Rule RIA, at pp. 53-4.
[18] Proposed Rule RIA, at p. 54.

Close to 100 percent of the $35.5 billion primary estimate of one-time costs and 89 percent of the $4.2 billion primary estimate of recurring compliance costs derive from the premarket review, 510(k), and De Novo requirements that would apply to LDTs within four years from FDA's publication of the final phaseout policy.[19]

II. The RIA's Estimate of the Proposed Rule's Costs

To put the Proposed Rule's one-time compliance costs in perspective, OEA's primary estimate of $35.5 billion is over 1.2 times their primary estimate of 2023 annual LDT revenues, which amount to $28.6 billion.[20] On average, publicly traded firms offering LDTs spend 64 percent of their revenue providing their services; the remaining 36 percent of revenue is the gross margin of the services before operating costs, such as overhead, salaries, research and development, and administrative expenses.[21] If one were to apply a gross margin of 36 percent (which significantly overstates the net economic margin from LDTs available to pay compliance costs) to OEA's primary estimate of 2023 annual LDT revenues, laboratories would be required to use nearly three and a half years of those gross margin profits on LDTs just to be able to cover the one-time compliance costs introduced by the Proposed Rule. And, as suggested, this does not even account for the fact that gross margin profits substantially overstate the actual cash after expenses that would be available to laboratories to pay for these newly introduced compliance costs. Moreover, these figures do not include the actual fees laboratories would need to pay to FDA to accompany their submissions for existing LDTs, which OEA estimates would total over $1.5 billion but are considered transfers since they represent revenue for FDA.[22] Perhaps most importantly, these costs represent just a fraction of the Proposed Rule's total potential costs.

A. Examining LDTs at Risk of Exiting the Market

In addition to compliance costs, explicitly considering countervailing risks or indirect costs is required by Circular A-4 and critical to gain a more complete understanding of the likely effects of the Proposed Rule.[23] This is especially true if the RIA is to allow stakeholders and the broader public to assess whether the benefits of the proposed rule justify its costs as Executive Order 12866 mandates.[24] OEA acknowledges the possibility that laboratories "may choose to exit the market or discontinue certain IVDs offered as LDTs due to compliance costs."[25] In

[19] Proposed Rule RIA, at p. 85.
[20] Proposed Rule RIA, at p. 27.
[21] Revenue and gross margin data were collected from publicly available information from Capital IQ for nine publicly traded laboratories that offer LDTs. The average gross margin weighted by revenue for these firms in 2022 was 36.2 percent, but gross margin does not take into account overhead, salaries, research and development, and administrative expenses. Moreover, this percentage represents an approximation, given that it considers a broader set of products and services than just LDTs. Measures of profits that account for operating expenses and opportunity costs are better measures to determine at-risk products or services. Despite the limitations of using gross margin, it is used throughout this analysis to be consistent with OEA's analysis of at-risk products in its Medication Guides: Patient Medication Information proposed rule.
[22] Proposed Rule RIA, at p. 94.
[23] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 26.
[24] Executive Order 12866, Regulatory Planning and Review, 58 FR 51735 (Oct. 4, 1993).
[25] Proposed Rule RIA, at p. 87.

addition, OEA suggests in the RIA an approach for estimating these costs by employing a similar methodology to what they utilized in their analysis of a previously published proposed rule, Medication Guides: Patient Medication Information.[26] Still, OEA indicates they are unable to estimate these indirect costs due to lack of data.

However, the information that is already presented in the RIA allows one to develop a sense of the magnitude of these costs. OEA's primary estimates for 2023 annual industry revenue and the number of LDTs on the market are $28.6 billion and 80,400 LDTs, respectively, suggesting that the average LDT generated $356,000 in annual revenue in 2023.[27] Even before considering the costs associated with performing these tests, it is instructive that the average LDT's annual revenue falls well below OEA's primary estimate of $4.38 million for a premarket application ("PMA") for approval as well as $565,000 for a De Novo classification request.[28] OEA estimates that FDA approval for a 510(k) submission ranges from $275,000 to $526,000 depending on the complexity of the study.[29] Therefore, many LDTs will have less annual revenue than the one-time cost for initial approval, and these costs ignore the actual fees paid by the laboratory to FDA, which is considered a transfer for purposes of OEA's analysis.

The large one-time costs for approval relative to the revenues for LDTs means that much of the industry is at risk of exiting the market. In their RIA assessing the economic effects of FDA's Medication Guides: Patient Medication Information proposed rule – which OEA indicated would inform their analysis for at-risk LDTs under the Proposed Rule[30] – OEA specified that the threshold for a product to be at risk is one that does not have enough sales "to cover the cost of [Patient Medication Information] without resulting in negative accounting profit."[31] OEA states, "For any product with positive annual sales less than its corresponding threshold…we determine that product to be at risk of exiting the market if it is not granted a waiver or extension of the requirements of [Patient Medication Information]."[32]

Applying OEA's threshold for at-risk products to the case of LDTs means tens of thousands of tests would be at risk even before considering that accounting profits are a fraction of the revenue they generate. Still, following OEA's proposed approach to focus on using gross margin to identify at-risk LDTs reveals even more clearly how much of the market would be at risk from the Proposed Rule. Assuming a gross margin of 36 percent, which, as described, represents a significant overestimate of the net economic margin from LDTs available to pay

[26] Proposed Rule RIA, at p. 88. OEA directs the reader to section II.G.1 "Count of At-Risk Products" in the Preliminary Regulatory Impact Analysis of the proposed rule Medication Guides: Patient Medication Information ("Medication Guide RIA"), (May 31, 2023) available at fda.gov/about-fda/economic-impact-analyses-fda-regulations/medication-guides-patient-medication-information-proposed-rule-preliminary-regulatory-impact.
[27] Proposed Rule RIA, at pp. 24-7.
[28] Proposed Rule RIA, at pp. 78, 81-4.
[29] Proposed Rule RIA, at pp. 81-3.
[30] Proposed Rule RIA, at p. 88.
[31] Medication Guide RIA, at p. 45.
[32] Medication Guide RIA, at p. 46.

compliance costs, the yearly gross profit for the average LDT is $128,160, still well below the cost of any approval process required by FDA.

Even considering the assumed sales growth rate used by OEA in the RIA, which would mean that the average LDT would generate $164,469 in gross margin by 2028, when all existing LDTs would be subjected to premarket review requirements, significantly more than 50 percent of tests would be at risk of no longer being offered employing OEA's established criterion. Stated differently, the gross profit of the average LDT would be less than 60 percent of the estimated cost of even the most cost-effective pathway to approval, the 510(k) with method comparison study, which requires a predicate device so is not likely to be an option for many LDTs. Moreover, this simple calculation does not even incorporate the fee that laboratories are required to pay as well as the reality that just as revenue may grow, so will the costs associated with preparing for the approval process.

Appealing to OEA's Tables A.2 and A.3 in Appendix A which contain estimates of LDT revenue and volume by firm size to support OEA's required analysis under the Regulatory Flexibility Act, one finds that the average LDT does not generate enough gross profit to avoid being at risk by OEA's definition for any category of firm size.[33] Assuming the same gross margin rate as before, average gross profit is $57,445 for LDTs from laboratories up to $100 million in annual revenue, and $259,541 for LDTs from laboratories over that size.

Those same data allow one to estimate the actual percentage of LDTs that may be at risk. Applying the assumed sales growth rate used by OEA in the RIA for LDT revenue and computing average gross profit across all size categories in 2028 when LDTs would be subject to the review requirements under the Proposed Rule, one can compute the estimated standard deviation of the distribution. Doing so and assuming LDT gross profits follow a normal distribution suggests that just over 90 percent of the universe of existing LDTs might be at risk because their gross profit is below the estimated cost of the 510(k) with method comparison study approach, even if costs are assumed to grow at only half the rate of revenues and OEA's estimate of the associated submission fee is weighted by firm size. And the associated percentage of LDTs at risk climbs to close to 95 percent if one simply applies OEA's 2023 data directly to perform the calculations, comparing the estimated 510(k) with method comparison cost including a weighted average of the associated submission fee against OEA's described distribution of laboratory LDT revenue.

Further, even these estimates understate the number of LDTs at risk since they rely on gross profit rather than operating profit or, even more accurately, economic profit. Gross margin does not incorporate the full set of costs facing a firm, such as overhead, research and development, and opportunity cost, that economic profit or even operating profit would consider. As OEA even notes in its RIA assessing the economic effects of FDA's Medication Guides: Patient Medication Information proposed rule, using gross profit "in the calculations results in

[33] Proposed Rule RIA, at pp. 124-6.

threshold [revenue] values that are smaller than if we were to use economic profit. Because of this, our estimates of at-risk products may represent lower bounds."[34]

B. Comparing Social Costs of At-Risk LDTs to the Proposed Rule's Benefits

In its computation of compliance costs, OEA assumes, without explanation, that only 50 percent of LDTs would require a premarket submission, with the other 50 percent exempt from the requirements. In fact, in the two places in the RIA where this assumption is stated, the other section is referenced, with no support provided in either place.[35]

Nevertheless, assuming this assumption is accurate, it would mean that 40,200 of the estimated 80,400 LDTs would require a premarket submission. To gain a sense of the magnitude of the health costs connected to the loss of roughly 90 percent of the existing stock of LDTs subject to approval under the Proposed Rule, one can apply OEA's estimates of the social value per case of an accurate diagnosis, which they use to value the benefits of the Proposed Rule. Much like FDA asserts in its analysis of the benefits of shifting from LDTs to FDA-approved tests in extending patient lives, an extensive medical literature highlights the critical role that LDTs play in delivering accurate diagnoses to save patients with potentially life-threatening conditions.[36] Thus, not having those potentially life-saving tests at all, or forcing medical personnel to shift to tests less appropriate for detecting the underlying condition accurately, can result in premature mortality in much the same way that having a more accurate test can extend a patient's life, as OEA suggests.

Applying OEA's computation for the social value per case of an accurate diagnosis, and assuming that each lost LDT results in just one additional life that is not extended on average because the test is no longer available that year, the annual health cost in 2022 dollars would be

---

[34] Medication Guide RIA, at p. 46.

[35] Proposed Rule RIA, at pp. 68, 75. In section II.F.2, OEA notes, "As described in section II.F.4, we estimate that 50% of IVDs require a premarket submission." In section II.F.4, OEA notes, "As mentioned in section II.F.2, we estimate that approximately 50% of IVDs currently undergo premarket review."

[36] See, e.g., Caliendo, Angela M., et al. "Maintaining Life-saving Testing for Patients with Infectious Diseases: Infectious Diseases Society of America, American Society for Microbiology, and Pan American Society for Clinical Virology Recommendations on the Regulation of Laboratory-developed Tests." *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* (2016) 63(2): 151-4; Dimmock, David, et al. "Project Baby Bear: Rapid Precision Care Incorporating rWGS in 5 California Children's Hospitals Demonstrates Improved Clinical Outcomes and Reduced Costs of Care." *The American Journal of Human Genetics* (2021) 108(7): 1231-8; Marzinke, Mark A., et al. "The VALIDity of Laboratory Developed Tests: Leave It to the Experts?" *Journal of Mass Spectrometry and Advances in the Clinical Lab* (2023) 27: 1-6; Ricker, Charité, et al. "Increased Yield of Actionable Mutations Using Multi-gene Panels to Assess Hereditary Cancer Susceptibility in an Ethnically Diverse Clinical Cohort." *Cancer Genetics* (2016) 209(4): 130-7; Rummel, Seth K., et al. "Should Genetic Testing for Cancer Predisposition Be Standard-of-Care for Women with Invasive Breast Cancer? The Murtha Cancer Center Experience." *Cancers* (2020) 12(1): 234; Sun Li, et al. "A Cost-effectiveness Analysis of Multigene Testing for All Patients with Breast Cancer." *JAMA Oncology* (2019) 5(12): 1718-30. The majority of genetic tests, as discussed in the referenced literature, are understood to be LDTs. *See,* (*"*The majority of genetic tests – a type of IVD that analyzes various aspects of an individual's genetic material (e.g., DNA, RNA) – are LDTs.") Sarata, Amanda K. *"*FDA Regulation of Laboratory-Developed Tests (LDTs)." *Congressional Research Service.* (December 7, 2022).

between $52.8 and $79.6 billion using OEA's central estimates. These calculations follow from multiplying the number of LDTs that would be at risk of exit based on OEA's stated threshold by the per case value of an accurate diagnosis, as described by OEA.[37] The variation in the computation results from whether the estimates of the value of a statistical life year are computed using either a three or seven percent discount rate. Further, these costs assume that OEA's estimates of how lives are extended through an accurate diagnosis – which they derive by focusing on cancer specifically – are applicable to a broader range of conditions for which LDTs are used.[38] Of course, this is precisely what OEA assumes in their analysis of the benefits of the Proposed Rule as well.[39]

The bottom line is that, under these relatively conservative assumptions, the annual health costs associated with at-risk LDTs leaving the market would easily surpass any savings associated with a reduction in one-time approval costs because those at-risk LDTs would not be subjected to premarket approval, given they were no longer being offered at all. Stated differently, if the proposed rule's one-time costs associated with premarket approval requirements were even reduced by 90 percent, equivalent to $32 billion, due to LDTs exiting the market, the resulting reduction would still be substantially less than the estimated societal costs from lives shortened in one year of $52.8 to $79.6 billion because of the Proposed Rule. And, unlike the one-time compliance costs, the costs associated with premature mortality from lost LDTs are recurring welfare costs, meaning these costs are incurred every year.

In the end, there is simply not enough LDT revenue dollars to move a significant portion of LDTs through the approval process. Given what OEA has proposed as the distribution of LDTs that would need PMA, 510(k), and De Novo approvals – the one-time submission costs and fees to get existing LDTs through approval would total $33.5 billion.[40] With only $28.6 billion in annual revenue and $10.3 billion in gross margin, at most there would only be enough revenue to move 2,238 of OEA's estimate of 4,020 LDTs through the PMA approval process before every single dollar of revenue would be exhausted – leaving 94 percent (or 37,962) of LDTs without any funds to attempt approval.[41] And this assumes that the 50 percent of LDTs, or

[37] Proposed Rule RIA, at pp. 33-7.
[38] Proposed Rule RIA, at pp. 33-40.
[39] Embedded in the assumption that each lost LDT is associated with just one additional life not extended is the reality that some LDTs extend many lives per year, and others may extend close to zero, either because there are comparable alternatives for the LDT, or the underlying condition will not shorten the individual's life. Also incorporated in this assumption is the recognition that all tests are imperfect, such that a small subset of lives shortened might not have been extended because of a test error (e.g., a false negative) had the test been performed.
[40] OEA estimates 4,020 of existing LDTs will go through PMA applications with $4.38 million in submission costs and $.23 million in fees to FDA; 4,020 LDTs will go through with De Novo classifications with $.56 million in submission costs and $.70 million in fees; 18,974 LDTs will go through 510(k) method comparison studies with $.27 million in submission costs and $.10 million in fees; and 13,186 LDTs will go through 510(k) moderately complex clinical studies with $.53 million in submission costs and $.10 million in fees. See Tables 25, 28, 29, 30 and 34 of the Proposed Rule RIA.
[41] Assuming the same gross margin rate as before, each PMA approval would need $12.79 in annual revenue to have enough proceeds to handle $4.38 million in submission costs and $.23 million in fees (($4.38 million + $.23 million)/.36 = $12.79 million). With total annual industry revenues of $28.6 billion, at most 2,238 LDTs could go through PMA before all remaining LDTs would be at risk ($28.6 billion/$12.79 million = 2,238).

40,200, that OEA claims would not need to go through the FDA approval process collectively do not earn a single dollar of revenue, obviously an illogical assumption.

Using the described cost estimation approach derived from data already presented in OEA's RIA, it becomes clear that at least one source of cost that OEA only discusses qualitatively actually exceeds the costs that are estimated. These costs associated with lost LDTs also exceed OEA's comparable estimate of the Proposed Rule's annual benefits, which amount to $26.8 billion with a three percent discount rate and $40.0 billion under a seven percent discount rate. Adding in the one-time benefits that OEA computes, which range from $4.1 billion to $6.8 billion using a three or seven percent discount rate respectively, the annual cost derived solely from lost LDTs would substantially exceed the benefits in any given year.

Further, the computation of the costs of lost LDTs presented here, whose size already exceeds the estimated benefits of the Proposed Rule, does not even consider the related costs of lost innovation for those LDTs that remain in the market. It is quite common for an LDT to be modified during the course of its use to improve the quality of the test and adapt to changing conditions. A 2018 study published in *JAMA Oncology* reported that more than 60 percent of the laboratory participants in their study of the relative performance of FDA-approved and lab developed oncology tests reported modifying their FDA-approved test "to broaden clinical practice, rendering them LDTs."[42] Under the Proposed Rule, these improvements would, in most cases, require FDA approval, thus significantly reducing the number of modifications that could be made given the financial costs and time connected to doing so.

C. Using Industry Evidence to Substantiate Estimated Costs from Lost LDTs

The described estimates associated with the potential for lost LDTs are consistent with data from laboratories competing in the LDT market. Responses from an informal survey of representative members of the ACLA revealed that the overwhelming majority of LDTs they offer gross less than $5 million in revenue per year. Using the previously described estimated gross margin percentage, annual gross profit for these tests thus amounts to several times less than OEA's estimate of the cost of taking any of these tests through the premarket approval process. In reality, annual revenue from most LDTs is much less than even this simple estimate might suggest. For example, one laboratory company reported that over 40 percent of the substantial set of LDTs that the company offers generate revenue less than even the fiscal year 2024 510(k) user fee of $21,760.

These data from industry participants reveal that the previously discussed calculations using OEA's data – which suggest both that a large majority of LDTs offered in the market would be at risk and that the associated welfare costs under FDA's proposed approach to oversight would be substantial – are decidedly reasonable. These at-risk assays would range from LDTs important in determining the care for patients with hematologic disease to those distinguishing rare forms of anemia from other blood conditions; and from tests used for the

[42] Kim, Annette S., et al. "Comparison of Laboratory-Developed Tests and FDA-Approved Assays for *BRAF*, *EGFR*, and *KRAS* Testing." *JAMA Oncology* (2018) 4(6): 838-841.

diagnosis of rare inherited metabolic diseases to tests available to help diagnose Rhett Syndrome, a rare neurological disorder that causes the loss of motor and language skills most commonly in girls.

In sum, by solely focusing on compliance costs in the RIA, OEA has failed to monetize a critical category of costs that has the potential for health effects resulting from LDTs exiting the market that substantially exceed the supposed benefits of the Proposed Rule. This represents a failure of the RIA to meet the standards outlined in Circular A-4 for economic analysis in rulemaking.[43] Conducting an RIA requires consideration of the direct and indirect effects of that regulation, including any potential unintended consequences of the proposal; moreover, an RIA must treat benefits and costs in a symmetric way in performing the analysis. Thus, it is not sufficient to simply consider possible health benefits associated with eliminating or reducing the number of, in FDA's words, potentially "problematic" LDTs without simultaneously considering the costs connected to the potential loss of welfare-enhancing and lifesaving LDTs that might no longer be offered. These costs arise because of the significant financial costs associated with complying with the regulatory framework relative to the revenue generated by laboratories in producing and performing LDTs.

III. The RIA's Estimate of the Proposed Rule's Benefits

Much like with the computation of costs, OEA's assessment of the benefits of the Proposed Rule also presents several issues. As described, over 98 percent of the total quantified benefits result from the Proposed Rule's suggested ability to reduce misdiagnoses from "problematic" LDTs. OEA estimates a baseline annual total of 19,000 fatal cases that receive a misdiagnosis due to "problematic" LDTs, all of which they claim would be prevented by the Proposed Rule. To reach that estimate, OEA starts with a primary estimate of 160,000 misdiagnosis fatalities associated with conditions other than heart disease. This figure is then reduced by 50.0 percent to account for testing that occurs outside of IVDs and then another 50.0 percent to account for testing done by IVDs that are not LDTs. Finally, of the remaining misdiagnoses attributable to LDTs, OEA assigns 47.4 percent as their estimate of the probability the misdiagnosis resulted from an LDT that is "problematic," yielding 19,000 misdiagnoses from "problematic" LDTs.[44] They determine that each misdiagnosis avoided has a benefit value of $1.46 million at a three percent discount rate and $2.2 million at a seven percent discount rate – resulting in aggregate annual benefits of $26.3 billion and $39.5 billion depending on the discount rate used.[45]

Among other issues in their computation of benefits, OEA does not adhere to established principles for preparing RIAs in two critical areas, which results in estimates of the health benefits of the Proposed Rule that are substantially inflated. First, the RIA makes inappropriate use of a benefit transfer approach to extrapolate benefits by using a single disputed study of LDT analytical accuracy, relative to including references to additional research that suggest the

[43] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 26.
[44] Proposed Rule RIA, at p. 39.
[45] Proposed Rule RIA, at pp. 37-40.

probability employed by OEA to measure the likelihood that an LDT is "problematic" is far too high. This is true both because the study they rely on is flawed and because the literature, more generally, reaches different conclusions. Second, OEA incorrectly assumes that every fatality resulting from a misdiagnosis due to a "problematic" LDT will be eliminated under the Proposed Rule – an assumption that is unsupportable and contradicted by the studies OEA relies on elsewhere in the RIA. As OEA itself asserts, "no test is perfect 100% of the time,"[46] and diagnosis is determined by leveraging clinical inputs beyond test results.

A. Evaluating the Appropriateness of OEA's Benefit Transfer Approach

One approach to valuing benefits in an RIA is to employ what is known as benefit transfer. Benefit transfer uses existing estimates of benefits from other studies and applies them to a new context, which in rulemaking means the context in which the rule is being contemplated. As described in Circular A-4, this method should "be treated as a last-resort option and not used without explicit justification" for a variety of reasons, including that the findings of the studies may pertain to a particular setting that is not reflective of the circumstances associated with the rulemaking.[47]

In evaluating studies to include, Circular A-4 advises that "selected studies should be based on adequate data, sound and defensible empirical methods and techniques." Moreover, populations represented in the research and the regulatory context should be similar, and the "market size (e.g., target population) between the study site and the policy site should be similar." For example, the Circular notes that "a study valuing water quality improvement in Rhode Island should not be used to value policy that will affect water quality throughout the United States."[48]

In the Proposed Rule, the assumption that is in large part responsible for the quantified benefits is OEA's estimate that 47.4 percent of LDTs are "problematic."[49] To arrive at that figure, OEA relies on a 2022 study published by Pfeifer et al. in the *American Journal of Clinical Pathology*, in which the authors examined performance for 19 laboratories employing LDTs to determine whether a patient was well-suited for a specific type of therapy for metastatic colorectal cancer.[50] The authors found that 9 of the 19 labs, or 47.4 percent, had five or more errors, which were predominately false negatives and which reflected an error rate greater than the statistical inaccuracy of a companion FDA-approved test. OEA then uses a benefit transfer approach to extrapolate from that result to assert that 47.4 percent of all LDTs are "problematic" and, thus, a significant number of lives associated with preventable misdiagnosis could be extended under the Proposed Rule.[51]

---

[46] Proposed Rule RIA, at p. 37.
[47] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 24.
[48] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 25.
[49] Proposed Rule RIA, at p. 38.
[50] Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-38.
[51] Proposed Rule RIA, at p. 38.

OEA's approach raises significant issues. It is inappropriate to use a single, small study focused on one disease to characterize the performance of all LDTs across all testing disciplines. Pfeifer et al. (2022) explicitly recognize in their research the issues in making a generalized extrapolation to a large population of laboratories from their work in suggesting, "our study consisted of a relatively small number of nonrandomly selected laboratories….These laboratories and their respective LDTs may not represent the broader landscape of laboratories that perform clinical NGS in CLIA-certified environments."[52]

Perhaps even more importantly, the Pfeifer et al. (2022) study is already outdated. A more recent 2023 analysis of the same SPOT/Dx pilot data by Zehir et al. (2023) concludes that the SPOT/Dx pilot had multiple design and analytic differences with established proficiency testing programs. After remedying those issues, the authors reach a fundamentally different conclusion, explaining that LDTs exhibit "excellent" analytical performance.[53] Zehir et al. (2023) explain that most of the false negatives reported by laboratories in the SPOT/Dx pilot were the result of variants being tested with mean variant allele fractions ("VAFs") below the participant laboratories' limit of detection ("LOD"). As the authors' note, under the CLIA standards, laboratories are only expected to detect and report variants with criterion standard VAFs at or above their laboratory's assay LOD. Once laboratories are evaluated against the test results they can be expected to detect and report, more than half of what OEA determines to be "problematic" LDTs are no longer "problematic." In fact, Table 3 of Zehir et al. (2023) indicates that only four of 19 LDTs reported five or more false negatives, not nine of 19 as reported by Pfeifer et al. (2022).[54]

Because OEA heavily relies on Pfeifer et al. (2022) in their estimates of benefits, this seemingly small change in the analysis of the SPOT/Dx pilot data has a large impact on the aggregate benefits of the Proposed Rule. Shifting from nine "problematic" LDTs to four of 19 LDTs – meaning 47.4 percent to 21.1 percent – cuts out over half of the expected health benefits

---

[52] Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-38, at p. 636.

[53] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at pp. 6-7. "Our analysis of the SPOT/Dx pilot results using methods modeled after established PT programs shows that, contrary to the reported conclusions of the original SPOT/Dx pilot, laboratory performance for KRAS and NRAS SNVs was excellent, both in wet and dry engineered samples. The overall detection rate for SNVs was 96.8%. The reanalysis confirmed that MNVs, although exceptionally rare or never observed in colorectal cancer, were detected at lower rates than SNVs, with an overall detection rate of 81.1%."

[54] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine.* (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at Table 3. Eliminating some of the tests from the analysis to account for tests that were below the participant's LOD could move the statistical z-score threshold of five or more test down to a lower number (e.g., four or more). Reevaluating the statistical threshold to account for this, none of the results change. All labs with four of less false negatives are not statistical different from the FDA-approved diagnostic.

of the Proposed Rule. With this correction, the aggregate benefits range from $11.7 to $17.6 billion, not $26.3 to $39.5 billion as reported in the RIA.

However, this is not the only problem that results from OEA's reliance on Pfeifer et al. (2022). Zehir et al. (2023) also note that a little over half of the false negative test results in the SPOT/Dx pilot were related to multinucleotide variants ("MNVs") that are extremely rare or never observed in reality. As Zehir et al. (2023) describe, "[a]nother important difference between the SPOT/Dx pilot and PT programs was the inclusion of a disproportionately high number of MNVs. KRAS or NRAS MNVs are so rare that there are no examples in the AACR GENIE dataset (public release v12) of 14,328 colorectal carcinomas, yet they comprised nearly a quarter (12/54; 22.2%) of the variants in the pilot."[55]

By extrapolating from Pfeifer et al. (2022), OEA is disproportionately relying on false negatives from extremely rare or never observed MNVs in colorectal cancer to then determine what portion of the general population of tens of thousands of LDTs are "problematic." This application of benefit transfer fails to adhere to the Circular A-4 principles on several dimensions, including choosing studies "based on adequate data, sound and defensible empirical methods and techniques," those in which the "study context and policy context…have similar populations," and those where the associated "good, and the magnitude of the change in that good [are] similar in the study and policy contexts."[56] As Zehir et al. (2023) notes, the type of generalizing employed in the RIA is even a problem in evaluating oncology testing, let alone all LDTs:

> *Results obtained from a small pilot study focused on one disease with rare or never-reported variants at low VAFs cannot be generalized to overall laboratory performance for all types of cancer. The pilot results only reflect laboratory performance for the study samples, which represent a minute percentage of samples encountered in routine clinical practice. As stated by Harada and Mackinnon, although the MNVs in the pilot "...serve the purpose of challenging a laboratory's informatics pipeline, they do not simulate a real-world situation," and the study design "...does not fully align with pan-tumor genomic analysis, which most laboratories are currently implementing."...The conclusions of the SPOT/Dx pilot about variable accuracy in the detection of genetic variants among some LDTs only apply to the samples with uncommon mutations at low-level VAFs included in the pilot and not to the performance of NGS LDTs overall.*[57]

Of the four remaining laboratories with alleged analytical accuracies significantly lower than the FDA-approved companion diagnostic, one of them had all of their false negatives derive

---

[55] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine.* (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at p. 8.
[56] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 25.
[57] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine.* (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at p. 9.

from the extremely rare or never observed MNVs that Zehir et al. (2023) and others conclude cannot be applied to real-world situations.[58] With this correction, only three remaining LDTs out of 19 demonstrate an analytical difference with the FDA-approved companion diagnostic. As a result, the benefits from OEA's extrapolation fall to a range of $8.8 billion to $13.2 billion, meaning that annual benefits are actually one-third of what was estimated by OEA.

B. Assessing the Benefits Associated with Shifting to FDA-Approved Tests

In addition to more accurately characterizing the extent to which "problematic" LDTs exist, OEA must also consider the analytical accuracy of FDA-approved tests relative to the baseline of no change in the regulatory framework to be able to adequately measure the benefits of the Proposed Rule. As described, OEA readily admits that no test is perfect, indicating "an IVD that yields a false result in an individual case is not necessarily a problematic IVD (indeed, no test is perfect 100% of the time)."[59] As a result, benefits from improved testing outcomes should be measured based on the incremental improvements in accuracy rates.

However, rather than evaluating incremental improvements, OEA's approach to measuring benefits assumes that all misdiagnoses from "problematic" LDTs will go away under the proposed regulatory regime. Still, the RIA provides no basis for this assumption nor is it at all supported in the medical literature. Moreover, the approach OEA employs, using the probability of being a "problematic" LDT in its benefit calculation, is unnecessary and simply adds a complicated assumption to try to estimate.

OEA could have avoided this step altogether simply by comparing the analytical accuracy of LDTs generally to FDA-approved diagnostics and used that as the basis for determining how many misdiagnoses could be avoided. For example, if LDTs have an analytical accuracy of 97 percent compared to 98 percent for FDA-approved diagnostics, then it would be reasonable to expect that roughly one-third of the misdiagnoses could be avoided (by moving from a three percent error rate to a two percent error rate).[60]

Academic studies, including those referenced in the RIA, find that the analytical accuracy differences between LDTs and FDA-approved diagnostics are actually not far apart and, as a result, suggest that benefits of the Proposed Rule are far lower than what OEA proposes. For example, in their study that appeared in *JAMA Oncology*, Kim et al. (2018) find a high rate of accuracy and comparable performance of LDTs and FDA-approved diagnostics for three

[58] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at p. 8. Laboratory 13 had eight false positives reported in Pfeifer et al. (2022), all of which were related to MNVs.
[59] Proposed Rule RIA, at p. 37.
[60] For example, assuming these assumptions about relative accuracy rates are correct, if there are 10,000 tests performed with LDTs, roughly 300 misdiagnoses would result. If, instead, those 10,000 tests were performed with FDA-approved diagnostics, roughly 200 misdiagnoses would result, suggesting a 33 percent reduction.

common oncology analytes: BRAF, EGFR, and KRAS. The overall accuracy for LDTs was 97.1 percent relative to 97.5 percent for FDA-approved diagnostics.[61]

Similarly, a 2019 study by Moncur et al. (2019) compares the performance of different assay methods on College of American Pathologists proficiency testing for variant analysis for BRAF, EGFR, and KRAS. Their findings demonstrate the high degree of accuracy and comparable performance across all laboratories, regardless of methodology. In fact, the authors report a percentage of acceptable proficiency testing for FDA-approved diagnostics of 97.5 percent and 97.2 percent for LDTs.[62]

Moreover, even Pfeifer et al. (2022) – the paper that OEA relies on for other aspects of its benefits calculation – notes that the FDA comparison is not analytically perfect, suggesting, "[t]he CDx has a published positive percent agreement of 98.7% and negative percent agreement of 97.6%."[63] Using the Zehir et al. (2023) reanalyzed data, the negative percent agreement rate of the LDT labs analyzed was 96.8 percent for single-nucleotide variants.[64]

Using estimates from these studies suggests the benefits of moving from LDTs to FDA-approved diagnostics could marginally improve analytical accuracy from 97.2 percent to 97.5 percent on the lower end – which would be expected to reduce misdiagnosis errors by 10.7 percent.[65] Or, on the high end, analytical accuracy could be improved from 96.8 percent to 97.6 percent using Pfeifer et al. (2022) and Zehir et al. (2023) – which corresponds with an expected reduction in misdiagnosis errors by 25 percent.[66] Applying these ranges to OEA's baseline annual estimate of misdiagnosis fatalities from LDTs suggests the resulting decreases in misdiagnoses correspond to only 22.6 percent or 52.8 percent of OEA's estimate, further indicating a substantial drop in benefits, which now range from $6.0 to $20.9 billion at the upper bound, corresponding to roughly a quarter to half of what OEA suggests.

---

[61] Kim, Annette S., et al. "Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing." *JAMA Oncology* (2018) 4(6): 838-41.

[62] Moncur, Joel T., et al. "Performance Comparison of Different Analytic Methods in Proficiency Testing for Mutations in the BRAF, EGFR, and KRAS Genes: A Study of the College of American Pathologists Molecular Oncology Committee." *Archives of Pathology and Laboratory Medicine* (2019) 143(10): 1203-11.

[63] Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-638, at p. 633.

[64] Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp, at pg. 4. The authors determined that under their reanalysis the number of false negatives associated with SNVs was 24 of 740 tests performed.

[65] Percent Reduction = (LDT Error Rate – FDA Error Rate)/LDT Error Rate; 10.7 percent = (2.8 percent - 2.5 percent)/2.8 percent.

[66] 25.0 percent = (3.2 percent - 2.4 percent)/3.2 percent. Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-38; Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp.

Importantly, in addition to being a more direct method and avoiding a need to unrealistically assume that FDA-approved tests have accuracy rates of 100 percent, the alternative approach described also considers a breadth of publications as the guidance in Circular A-4 suggests an agency applying benefit transfer should do, relative to using just one disputed study. Moreover, the estimates of lives extended are consistent with the described corrected analysis using a combination of Pfeifer et al. (2022) and Zehir et al. (2023).[67]

IV. Other Important Considerations in Preparing the RIA

In addition to computing benefits and costs of the Proposed Rule, agencies are required in preparing an RIA to assess reasonable alternative regulatory approaches. In doing so, the agency must evaluate the benefits and costs, both quantitatively and qualitatively, of the main alternatives identified by the analysis in addition to its proposed rule. Moreover, because benefit-cost analysis focuses on economic efficiency and can obscure how benefits and costs are allocated among different sub-populations, Circular A-4 further directs agencies to "provide a separate description of distributional effects…so that decision makers can properly consider them along with the effects on economic efficiency."[68] Distributional effects should be "described quantitatively to the extent possible" when they "are thought to be important."[69]

A. Considering Reasonable Alternatives to FDA's Preferred Approach

According to Circular A-4, alternatives that the agency "should consider" include contemplating different approaches to enforcement, varying the level of stringency, utilizing different regulatory instruments, particularly those that do not involve design standards and direct controls, and applying different standards for different types of regulated entities including those based on size or geography.[70] Consideration of alternatives is particularly important for FDA's Proposed Rule because, as described, its considerable costs, both in complying with the rule as well as the associated health effects from at-risk LDTs, raise questions around whether the benefits justify the costs.

In its assessment of alternatives in its RIA, OEA primarily focuses on variation in the timeline for compliance. In fact, these are the two alternatives for which the analysis provides quantitative estimates of both benefits and costs.[71] The first alternative shortens the phaseout period while the second alternative lengthens it. Because the regulatory approach otherwise remains the same, the computed changes in benefits and costs derive primarily from differences in when they are realized and the associated effects of discounting. As a result, the quantitative

[67] Pfeifer, John D., et al. "Reference Samples to Compare Next-generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics." *American Journal of Clinical Pathology* (2022) 157(4): 628-38; Zehir, Ahmet, et. al. "SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance." *Archives of Pathology & Laboratory Medicine*. (September 30, 2023) doi.org/10.5858/arpa.2023-0322-cp.
[68] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 14.
[69] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 14.
[70] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 7-9.
[71] Proposed Rule RIA, at p. 97-100.

estimates are qualitatively similar to those for the Proposed Rule. Any analysis implementing the previously discussed recommendations to reassess the benefits and account for health-related costs connected to lost LDTs would yield quantitative estimates similar to what is described in this letter. For these reasons, focusing on the timeline for compliance is not all that helpful as a pathway to suggest meaningful alternatives that foster transparency and public participation in the rulemaking process for the Proposed Rule.

A developed academic literature on regulatory politics and policy has examined the breadth of regulatory instruments agencies may consider that can improve upon the limitations of more traditional, direct controls, of which FDA's Proposed Rule is one example.[72] One of these approaches, management-based regulation or enforced self-regulation, requires regulated entities to develop plans to manage risks associated with their operations to flexibly achieve regulatory objectives.[73] After developing their plans, these same organizations are required to receive the associated regulator's approval. From the regulator's perspective, employing management-based regulation is most appropriate when the regulated community is characterized by a large number of heterogenous entities with regulated outputs that are difficult to observe and monitor. This is a set of circumstances that aptly characterizes the environment in which LDTs are developed and employed.

It is notable that the current framework utilized by CMS under CLIA to oversee laboratories, including those that develop LDTs, has elements of a management-based regulatory framework. Moreover, it is an approach that is actually employed by FDA itself in at least one other similar context, food safety regulation.[74] For example, CMS' regulatory approach focuses attention on the operations of the laboratory and qualifications and training of the associated staff. It imposes on laboratories the requirement that they develop and implement quality control procedures "to monitor the accuracy and precision of the complete testing process."[75] Through its Individualized Quality Control Plan (IQCP) program, laboratories also have the opportunity to tailor their quality control plans to the realities of their "unique testing environments and patients."[76]

---

[72] See, e.g., Carrigan, Christopher, and Cary Coglianese. "The Politics of Regulation: From New Institutionalism to New Governance." *Annual Review of Political Science* (2011) 14: 107-129; Richards, Kenneth R. "Framing Environmental Policy Instrument Choice." *Duke Environmental Law & Policy Forum* (2000) 10(2): 221-286.

[73] Ayres, Ian, and John Braithwaite. *Responsive Regulation: Transcending the Deregulation Debate*. New York: Oxford University Press (1992); Bardach, Eugene, and Robert A. Kagan. *Going by the Book: The Problem of Regulatory Unreasonableness*. Philadelphia: Temple University Press (1982); Coglianese, Cary, and David Lazer. "Management-Based Regulation: Prescribing Private Management to Achieve Public Goals." *Law and Society Review* (2003) 37(4): 691-730.

[74] Coglianese, Cary, and David Lazer. "Management-Based Regulation: Prescribing Private Management to Achieve Public Goals." *Law and Society Review* (2003) 37(4): 691-730.

[75] CMS, CLIA Individualized Quality Control Plan: Considerations When Deciding to Develop an IQCP (Nov. 2014), available at cms.gov/regulations-and-guidance/legislation/clia/downloads/cliabrochure12.pdf, at p. 1; CMS, CLIA Individualized Quality Control Plan: What is an IQCP? (Nov. 2014), available at cms.gov/regulations-and-guidance/legislation/clia/downloads/cliabrochure12.pdf.

[76] CMS, CLIA Individualized Quality Control Plan: Considerations When Deciding to Develop an IQCP (Nov. 2014), available at cms.gov/regulations-and-guidance/legislation/clia/downloads/cliabrochure12.pdf, at p. 1.

In so doing, the current regulatory framework employed by CMS for LDTs shares similarities, both in its design as well as in the characteristics of the associated regulated laboratories, to other US contexts in which regulators are currently employing management-based regulation effectively. These include the aforementioned FDA and the US Department of Agriculture's Food Safety Inspection Service for food production and the Occupational Health and Safety Agency for industrial chemical manufacturing to promote safe operations in their respective policy domains.[77] Thus, CMS' current approach to regulating LDTs is certainly not without precedent in similar contexts. CMS' regulatory approach adds additional elements as well. For example, in the current regulatory environment, LDTs are also subjected to proficiency testing to ensure analytical validity and periodic CMS laboratory inspections that are characteristic of some, but not all, management-based regulatory environments.

Beyond considering variation in the compliance timeline, OEA also briefly describes but does not attempt to quantify net benefits for two other regulatory approaches that would still phase out the existing general enforcement discretion approach for LDTs with respect to certain regulatory requirements connected to the Proposed Rule, including registration, listing, and adverse event reporting.[78] Moreover, they would still mandate that new LDTs as well as existing LDTs that undergo changes receive FDA approval. However, they would not subject LDTs in existence at the time of the final rule to premarket review requirements. In addition, the second of these two regulatory alternatives would also continue general enforcement discretion for LDTs that receive approval from the New York State's CLEP, even LDTs developed after the final rule.[79]

One attractive element of these latter two alternatives is that they consider the economic market failure the Proposed Rule attempts to address and tailor the approach to more specifically remedy that issue. Although not identified by OEA, the market failure in this case is asymmetric information, which as described in Circular A-4, suggests "informational remedies will often be preferred," as they provide "consumers a greater choice than a mandatory product standard or ban,"[80] which is what FDA is instead proposing. For example, by exempting many LDTs from premarket review requirements while retaining labeling requirements under stage two, FDA can specifically address the failure using a relatively lower cost approach, as OEA's primary estimates of $2.75 million in one-time and $220,000 in recurring compliance costs associated with the labeling requirement suggest.[81]

Much like the Proposed Rule, quantifying the benefits and costs of these two alternatives exempting existing LDTs from premarket review would likely still yield negative net benefits, at least after accounting for the sizable indirect costs associated with at-risk LDTs and a more reasonable application of benefit transfer in assessing the implications of eliminating "problematic" LDTs. However, the magnitude of the imbalance between costs and benefits is

[77] Coglianese, Cary, and David Lazer. "Management-Based Regulation: Prescribing Private Management to Achieve Public Goals." *Law and Society Review* (2003) 37(4): 691-730.
[78] Proposed Rule RIA, at p. 100-3.
[79] Proposed Rule RIA, at p. 102-3.
[80] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 9.
[81] Proposed Rule RIA, at p. 66.

almost sure to shrink, meaning that net benefits will be relatively less negative, given they avoid the one-time compliance costs associated with the proposed rule. OEA assumes that the one-time compliance costs would be eliminated through these regulatory approaches because they largely exempt existing LDTs from premarket review, 510(k), and De Novo requirements.[82] Further, at least for the first of these two alternatives, OEA estimates that ongoing annual costs would be between 51 and 58 percent of those associated with the Proposed Rule.[83]

Presenting a full analysis of the benefits and costs of these alternatives should not be overly difficult for OEA, given that many of the elements of that analysis are already available. For example, considering the alternative that would exempt from premarket review requirements existing LDTs as well as new LDTs that have obtained New York State approval, the primary source of uncertainty would be in estimating the proportion of new LDTs that would opt for approval under New York's CLEP rather than FDA's premarket approval processes.[84] This information could be derived by comparing the relative costs of FDA and CLEP test approval, the latter of which is publicly available.

Even absent these data, a conservative analysis could simply assume, as OEA's existing discussion in the RIA suggests, that this alternative would not impose compliance costs on the proportion of LDTs that opt to submit to CLEP in the existing environment. Assuming the remaining LDTs would be indifferent between undergoing FDA or New York State approval processes, the analysis can proceed by developing the key elements associated with the analysis of the Proposed Rule for these remaining tests. This includes estimating the number of new LDTs that would be at risk and the associated health costs, the compliance costs imposed on those that would still be offered, and the benefits associated with FDA or New York State approval with regard to the possibility for fewer false negative tests.

B. Separately Evaluating the Distributional Effects of the Proposed Rule

Often those who bear the costs of a regulation are not the same as those who enjoy its benefits. Moreover, a simple focus on net benefits in an RIA does not allow a policymaker the ability to consider distributional effects in their decision calculus. To account for this, Circular A-4 directs agencies preparing RIAs to analyze the distributional effects of the proposed rule as well. The phrase "distributional effect" references the effect a proposed rule has on sub-groups of the population or economy, including groups divided by income, race, sex, industry, or geography.[85]

OEA's RIA offers limited discussion of distributional effects. The RIA does note that existing health inequities could be exacerbated or ameliorated. However, it fails to address with

[82] Proposed Rule RIA, at p. 101.
[83] Proposed Rule RIA, at p. 97.
[84] Proposed Rule RIA, at p. 102-3. With this alternative, OEA also considers the possibility that some laboratories might consider opting for FDA's Third Party review program for 510(k) submissions but suggests the fees are comparable to FDA's approval fees.
[85] OMB, Circular A-4: Regulatory Analysis (Sept. 17, 2003), at p. 14.

any specificity the sub-groups that are at risk.[86] Still, it seems clear that a disproportionate amount of the Proposed Rule's costs will be imposed on vulnerable individuals, including those with rare diseases, low-income individuals, and racial minorities.

If finalized, the Proposed Rule will lead to consolidation in the testing market and reduced competition as LDTs are forced to leave the market as they are no longer economically feasible. It is notable that the effect of the Proposed Rule on LDT prices receives limited attention in OEA's RIA, with brief qualitative discussions in only a few places in the document.[87] Yet, for the LDTs that can remain in the market, providers will be forced to raise prices to handle the additional burden of significant additional compliance costs to allow those LDTs to remain economically viable.

As prices rise for health care services, including diagnostic tests, the law of demand assures that a measurable decrease in demand will occur for those services (even for insured individuals).[88] Importantly, low-income individuals with higher price elasticities will bear more of the burden of the Proposed Rule by taking on more of the mortality costs from price increases, as they cut back on using medical services.[89]

Similarly, those patients that are uninsured will most feel the impact of higher prices and will be more likely to opt out of diagnostic testing. Rates of uninsurance disproportionately concentrate on minority individuals and communities. For example, the US Census estimates that 8.3 percent of Black and 17.9 percent of Hispanic individuals do not have insurance, relative to 4.9 percent for White individuals.[90] Perhaps those most at risk under the Proposed Rules are the vulnerable individuals that fall in subgroups of people with rare diseases. Lower volume tests will be most at risk of market exit, reduced competition, and price increases.

In light of the large compliance costs relative to the revenues of LDTs, to fulfill its obligations under Circular A-4, it would seem that OEA must evaluate the distributional effects of the Proposed Rule to a much greater extent than they currently do, taking into account declines in market access to LDTs and changes in demand for services from increases in prices. This is perhaps even more important given OIRA's recent emphasis on broadening participation in the regulatory process in response to President Biden's Executive Order 14094, especially among traditionally underserved communities such as those that will be significantly affected by the Proposed Rule.[91]

---

[86] Proposed Rule RIA, at p. 106.
[87] Proposed Rule RIA, at p. 88-9, 106.
[88] Ellis, Randall P., et al. "Health Care Demand Elasticities by Type of Service." *Journal of Health Economics* (2017) 55: 232-243.
[89] See, e.g., Anderson, Michael, et al. "The Effect of Health Insurance Coverage on the Use of Medical Services." *American Economic Journal: Economic Policy* (2012) 4(1): 1-27.
[90] United States Census Bureau, Current Population Reports: Health Insurance Coverage in the United States: 2022 (September 12, 2023), available at census.gov/library/publications/2023/demo/p60-281.html.
[91] OMB, Request for Comments on Guidance Implementing Section 2(e) of the Executive Order of April 6, 2023 (Modernizing Regulatory Review), 88 FR 20916, (Apr. 7, 2023); Executive Order 14094, Modernizing Regulatory Review, 88 FR 21879 (Apr. 11, 2023).

V. Conclusion

OEA's RIA to accompany FDA's Proposed Rule fails in certain important areas to adhere to best practices as described in OMB's Circular A-4, as well as the accompanying literature considering the application of benefit-cost analysis to regulatory issues, which has substantial implications for the resulting estimates of benefits, costs, and distributional effects. Specifically, the analysis fails to:

1) quantify key ancillary costs with available data;
2) select and interpret studies in a sound manner to apply benefit transfer;
3) consider and quantify the effects of reasonable regulatory alternatives; and
4) recognize and quantify key distributional effects.

These limitations of the RIA lead to an analysis that significantly overstates the likely benefits, substantially understates the likely costs, and minimizes the potential substantial distributional effects of FDA's Proposed Rule. Remedying these issues by employing approaches outlined in this letter, as well as others, will allow OEA's RIA to demonstrate more accurately whether the benefits of the Proposed Rule justify its costs, ascertain if alternative approaches could better achieve FDA's goals at a lower cost, and offer a more transparent account of the Proposed Rule's likely impacts on those affected and other interested parties.