ARUP LABORATORIES
A nonprofit enterprise of the University of Utah and its Department of Pathology

500 Chipeta Way
Salt Lake City, UT 84108
800-522-2787
aruplab.com

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

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

This letter of public comment is provided on behalf of ARUP Laboratories, a non-profit enterprise of the University of Utah Department of Pathology. ARUP urges the FDA to withdraw the proposed rule "Medical Devices; Laboratory Developed Tests" (Docket No. FDA-2023-N-2177) for the reasons outlined in the collaborative letter below and our overriding concern that the proposed rule, as outlined, will present an undue burden on the clinical laboratory community, and it will negatively impact the patients it is attempting to protect.

Executive Summary

- The FDA proposal will reduce, an in many cases eliminate, access to safe and essential testing services, particularly for patients with rare diseases.
- Laboratory-developed tests are not devices as defined by the Medical Device Amendments of 1976, nor are clinical laboratories acting as manufacturers.
- The FDA does not have the statutory authority to regulate laboratory-developed tests.
- The FDA does not have the authority to regulate states, or state-owned entities. This is particularly relevant for the proposed rule regarding academic medical centers.
- The FDA's regulatory impact analysis is flawed in its design, source information, methods, and conclusions, and it systematically overestimates purported benefits of the proposed rule and dramatically underestimates its cost to society, the healthcare industry, and the ability to provide ongoing essential laboratory services to patients.
- The proposed rule would significantly limit the ability of clinical laboratories to respond quickly to future pandemic, chemical, and/or radiologic public health threats.
- The proposed rule would not be easily implementable, and it would create an insurmountable backlog of submissions that would hinder diagnostic innovation.
- The proposed rule limits the practice of laboratory medicine.
- The FDA has not evaluated less restrictive, easily administered alternatives, such as CLIA reform. This is particularly relevant for common test modifications used in most hospital and academic medical center settings.

Introduction

ARUP operates the hospital and outpatient clinical laboratories of a large academic medical center (AMC) – University of Utah Health. It is also the nation's largest non-profit clinical reference laboratory, with over 2,000 community hospital and AMC customer laboratories in all 50 states. ARUP processes more than 25 million specimens annually and has over 4,000 employees, with a menu of over 3,000 tests and test combinations. Since its founding nearly 40 years ago, ARUP has been among the safest and most innovative diagnostic laboratories in the nation. Our team of over 100 board-certified medical directors includes MD and PhD scientists with extensive medical and scientific expertise to guide the development and interpretation of tests, to ensure that our testing menu meets the ongoing clinical needs of health care providers, and to provide clinical consultations regarding test ordering and interpretation.[1]

The ARUP Institute for Clinical and Experimental Pathology is the research and development (R&D) arm of the organization, with over 60 R&D scientists actively engaged in test development and optimization in collaboration with our medical directorship. Over several decades, the R&D institute has developed, validated, verified, improved, and maintained several thousand tests including at least 1,500 laboratory developed tests (LDTs). Consistent with our academic foundations and our commitment to sharing knowledge with the clinical laboratory community, ARUP scientists and medical directors publish more than 120 manuscripts annually (over 3,400 scientific and clinical manuscripts in peer-reviewed journals to date) based on these and other activities.[2] Of significance to the proposed rule, many of these publications have documented superior performance of LDTs over FDA-cleared/approved assays or have described LDTs that fill an important unmet need in medical practice.

ARUP also has extensive laboratory expertise in clinical laboratory regulations and has closely followed and provided perspective in the peer reviewed literature on prior regulatory reform efforts regarding LDTs. This includes LDT risk stratification analysis,[3] review of regulatory and legislative records,[4] explanations of how LDTs are used across different laboratory settings,[5] regulatory implications of test modifications,[6,7] frequency of LDT use in clinical settings,[8] regulatory portrayal of LDTs during the COVID-19 pandemic,[9] and the impact of proposed regulations on clinical laboratories and the broader provision of healthcare services, including access to high quality and necessary testing for patients.[10] We have always prioritized sharing this research and perspective in the peer reviewed literature to ensure that others have access to real-world information regarding the clinical impact of proposed frameworks or initiatives.

ARUP has been continually certified under the Clinical Laboratory Improvement Amendments (CLIA) to perform high-complexity testing. We are accredited by the College of American Pathologists Laboratory Accreditation Program, the New York State Department of Health Clinical Laboratory Evaluation Program, and we are ISO 15189 CAP Accredited – all of which illustrate our profound commitment to quality and outstanding patient care. As such, doctors and health systems across the country often refer their most challenging cases to ARUP. All of our tests (including LDTs) have been extensively validated consistent with the regulatory requirements set forth under CLIA and our accrediting agencies. This collective effort and regulatory compliance help to ensure that our tests are safe, effective, and provide essential diagnostic information for patients and their providers. The FDA's Manufacturer and User Facility

Device Experience Database (MAUDE) – which tracks adverse events related to in vitro devices – contains no instances of an ARUP testing failure, which is a testament to the collective work of our teams.

Indeed, ARUP has a profound commitment to quality and patient safety across our entire organization. It is the primary motivator for our workforce and the foundation of our organizational pillar to "Provide Excellent Patient Care". We believe our LDTs are safe, effective, innovative, and designed to address gaps in existing commercially offered tests. While we agree that poor quality testing – LDTs or FDA-cleared/approved assays – should not be on the market or ever used for patient care, it is also important to emphasize that an overly burdensome regulatory framework would have a profoundly negative impact on the availability of safe and effective testing for patients in the U.S. We are further concerned that the proposed rule, as described, would have a disproportionately adverse impact on testing for rare disorders, underserved populations, and initiatives associated with personalized medicine such as oncology.

There is also significant legal uncertainty on whether the FDA has the statutory authority from Congress to advance the proposed rule and treat LDTs the same as manufactured medical devices. Additionally, we believe that the proposed rule and regulatory impact analysis have fundamental flaws on several legal, regulatory, operational, and medical grounds. As such, it is concerning that the rule has been advanced for public comment, given that the FDA has had ample time to foster a more thorough and collaborative understanding of the clinical laboratory community that it is proposing to now regulate.

Examples of our concerns are presented below. We believe that the proposed rule is fundamentally flawed and would lead to a profoundly negative impact on patient care if implementation was attempted as described. Furthermore, given the discordance between manufacturing and clinical laboratory operational environments and requirements, it is likely that any attempt at implementation would ultimately be chaotic and unsuccessful. This would lead to significant and material damage to the clinical laboratory community and the ability to care for patients in our respective settings.

Patient Safety and LDTs

As noted above, ARUP's primary focus is on patient safety and the quality of services that we provide. This same priority is shared by all our clinical laboratory colleagues, clients, and academic and clinical partners across the healthcare community. Our clients can trust the quality of our LDTs just as much as they can trust the quality of our FDA-cleared/approved assays – and that trust comes from decades of experience in developing tests, using them in our laboratory, and in consultation with clinicians for the care of their patients.

One important factor related to patient safety is the benefit of direct access to information that a clinical laboratory possesses when developing and performing an LDT, and the challenges that can be inherent to troubleshooting FDA-cleared/approved assays when problems arise. FDA-cleared/approved assays can be significantly more difficult to troubleshoot than LDTs due to the need for active collaboration from the manufacturer. With FDA-cleared/approved assays, a laboratory is often dependent upon an external vendor to acknowledge that a problem

exists, and then to remedy that problem if or when the issue is acknowledged. Additionally, while the FDA maintains a voluntary MedWatch reporting system for device-related issues, it is often not apparent to the submitter what improvements – if any – are enforced by the FDA or made by vendors based on these voluntary reports. Thus, while the 'locked down' nature of FDA-cleared/approved assays may have certain benefits; it also has vulnerabilities for clinical laboratories and patients alike. The vulnerabilities and challenges that laboratories face when using FDA-cleared/approved assays are not factored into the FDA's regulatory impact analysis, nor in a benefit analysis of LDTs, thus the regulatory impact analysis is limited and incomplete in nature. Additionally, the FDA does not acknowledge existing accreditation requirements under CLIA-deemed agencies that clinical laboratories currently are responsible for to respond to patient and client concerns with both FDA-cleared/approved assays and LDTs.

The FDA's narrow framing of public health challenges regarding false-positives, false-negatives, and screening tests unfortunately blurs the distinction between how a test performs, and how clinicians use test results, and it also presumes that labeling requirements fully address issues with utilization. Indeed, several issues as noted in the regulatory impact analysis reflect how a test is used, and not actually how the test performed. In its proposed rule, the FDA states that "through increased oversight, the public, including patients and healthcare professionals, could have more confidence that the test results they rely on are accurate" (section III.B.3). What is omitted from this statement is the detrimental impact on public health that would occur if an overly burdensome regulatory framework was applied – one that clinical laboratories could not reasonably afford.

It is therefore reasonable to conclude that the proposed rule, contrary to the assertions of the FDA, would directly lead to a reduction of existing and future safe and essential testing, thus having an adverse impact for patients across the nation. That impact would be felt mostly by patients with rare diseases, for diagnostics where reimbursement does not justify the commercial manufacture and distribution of conventional IVDs, and for testing associated with the emerging field of precision medicine. If patients lose access to tests, or if testing can only be performed at a small number of reference settings, this will delay diagnoses and treatment decisions. Worse yet, some disorders may go undiagnosed altogether. As a result, the very patients the FDA intends to protect under this proposed rule will instead be harmed by it.

We are also concerned about patient safety risks with the potential consolidation of LDT testing to a few reference settings. While market consolidation typically increases costs to patients, it also raises supply chain concerns regarding what happens when a company faces critical reagent or personnel shortages. In the current clinical laboratory market, those risks are reduced with LDTs being performed across different hospital settings. Under the proposed rule, those supply chain risks would be magnified.

The issue of patient safety also raises a broad public policy question – what should federal officials charged with protecting patients and the public do to avoid the potential for unsafe testing? In its proposed rule, the FDA has unilaterally asserted that it alone can rid the market of LDTs that it broadly asserts are unsafe. But instead of focusing on high-risk tests or bad actors, the FDA is claiming complete oversight of an entirely new category of entities in a

manner that will overwhelm its own ability to administer the current and proposed oversight. Is the FDA the right federal agency to regulate the fundamental aspects of LDTs?

While the FDA has the authority to regulate medical devices, a less restrictive and more easily administered method of LDT oversight is the pre-existing structure for LDTs under CLIA. Clinical validity could easily be addressed under notice and comment rulemaking and/or legislative updates to CLIA. In fact, it is already required by several CLIA-deemed accrediting agencies including the College of American Pathologists (CAP)[11] and the New York State Department of Health (NYSDOH).[12] CLIA law simply needs to be updated to reflect what its deemed agencies are already doing.

It should also be noted that CMS also has the authority under CLIA to gather critical evidence missing from the FDA proposed rule and regulatory impact analysis, including the extent of LDTs currently used by clinical laboratories. CMS already collects information about assay manufacturers in CLIA permit application forms.[13] Additionally, CAP accredited laboratories already maintain a list of all LDTs performed within their laboratories,[14] and laboratories accredited by NYSDOH must submit LDTs for review and approval prior to their use in the laboratory.[15] The data for LDTs in use in the U.S. already exists and could be easily obtained with minimal draft guidance under CLIA. A new regulatory framework for LDTs is not required to obtain this information, given this less restrictive, easily administered alternative.

Lack of Regulatory Authority Over LDTs

LDTs are Not Devices

The statutory definition of a device neither explicitly nor implicitly covers tests or assays. Section 321 of Title 21 United States Code defines the term "device" for the purposes of FDA regulation as:

> *"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is… (B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals…"*[16]

The definition does not *explicitly* cover tests. The statute does not include the word 'test' nor 'assay' as covered devices. It is reasonable to presume that Congress was aware, when writing this definition, that diagnostic tests are key elements of medical diagnoses. If they had intended to cover tests, they would have included them in the text of the Medical Device Amendments of 1976 (MDA). Moreover, the definition also does not *implicitly* cover tests. The inclusion of the term 'in vitro reagent' demonstrates clearly that Congress did not, in fact, intend to treat tests as devices. While the definition allows FDA authority to regulate a device and "any component" thereto, Congress makes clear they are regulating from the primary item to smaller components of that item. This will be further described below.

In the field of medicine and laboratory testing, in vitro reagents are used as components essential for laboratory testing. Because an in vitro reagent is just a component of a test under the statutory definition, it would be nonsensical for FDA to reason that tests are therefore

devices. Logic confers that if Congress intended to regulate tests, and in vitro reagents are components of a test, then Congress would have instead listed 'test' instead of in vitro reagent explicitly in the definition of device.

This can be illustrated more easily through a simple hypothetical example. Using the 'any component' structure of the statutory definition of device, if Congress had listed 'automobiles' as a device, FDA would indeed have the authority to regulate 'tires' because they are a *component* of an automobile. Conversely, if Congress listed 'tires' as a device, FDA would *not* have authority to regulate automobiles because they are not a component of a tire. Yet, that is precisely the flawed logic FDA applies in its current LDT proposal.

We therefore do not concur with the FDA's assertions in the proposed rule that it has regulatory authority over LDTs. As further evidence, and as extensively outlined in a comprehensive review of the regulatory history of LDTs,[17] the concept of LDTs was not even discussed in any Congressional hearings prior to the passage of the Medical Device Amendments of 1976 (MDA), nor does the MDA specifically address or describe LDTs. If Congress had intended to provide the FDA authority over LDTs, it would have been clearly described and outlined that authority in the legislation, which it clearly and undeniably did not.

It should also be noted that under existing FDA regulations (21 CFR 807.65) licensed practitioners (including physicians) are exempt from device establishment registration when they use such devices for their professional practice [subpart d] and clinical laboratories are similarly also exempt from device establishment registration [subpart i].[18] Requiring clinical laboratory registration would also be duplicative of the registrations and fees already required under CLIA.[19] The impact of the proposed rule on the practice of medicine is discussed further in a separate section later in this public comment letter.

Regulatory Authority Over Systems

We are also concerned about the FDA's reliance upon the term 'systems' as outlined in the proposed rule. The FDA describes systems as IVDs (section III.A; also section V.B.1.), presumably consistent with the definition of an 'in vitro diagnostic product' as introduced through rulemaking in 1973.[20] What is not shared, however, is that the definition of 'device' that was subsequently passed by Congress in 1976 specifically did *not* include the term system.[21] Given the FDA's reliance on the term system as a purported legal basis for its regulatory authority, this discrepancy justifies further significant administrative and/or judicial consideration prior to advancing any proposed rules.

Interstate Commerce and Commercial Distribution

The FDA's interpretations of 'interstate commerce' and 'commercial distribution' are also concerning, as they deviate from plain language definitions of these terms. For example, regarding interstate commerce (section V.B.3.a.), the FDA's concept is so expansive as to negate the entirety of the meaning of the word interstate. If Congress did not intend to restrict FDA authority to interstate commerce, it would not have used that term in the legislation.

The FDA (section V.B.3.b.) also convolutes the plain language meaning of commercial distribution to expand its meaning to purportedly reflect the broader term 'on the market'. If

Congress intended the MDA to reflect oversight over all IVDs on the market, it would have used that specific terminology. LDTs, however, are not objects nor are they distributed or shipped outside of the laboratory in which they are performed. Interestingly, the FDA subsequently reverts to the plain language concept of 'distributed' (section VI.B.3.; "distributed outside that laboratory") in its description of certain settings where limited QSRs may be implemented. The FDA in the proposed rule is therefore illogical and inconsistent in its own terminology, and it uses expansive definitions only when it supports its own claims for increased regulatory authority. Lastly, it should be noted that internal transfer "between establishments within the same parent, subsidiary, and/or affiliate company" is actually excluded from the definition of commercial distribution under current regulations (21 CFR 807.3).[22]

States are Not Persons

A recent HHS internal legal analysis *Federal Authority to Regulate Laboratory Developed Tests* provided a review of potential FDA authority over LDTs that was presented to the FDA commissioner in June of 2020.[23] While it was intended to remain confidential, this review has been cited in subsequent public reports,[24] and it is publicly available for download on the internet.[25] Many of its conclusions do not align with the current assertions presently being advanced by the FDA in the proposed rule. Discrepancies should be resolved prior to advancing any proposed rules. While the HHS legal analysis discusses several of the concerns noted above, including interstate commerce and commercial distribution, we specifically call out another discussion in this report in that the FDA likely has limited to no authority over regulating states and state-owned entities. For example, in the 2020 HHS legal analysis, the following is written,

> *"…FDA's registration, premarket review, and adverse event reporting requirements would not, if challenged by a sophisticated litigant, likely apply, as a matter of law, to any state-owned laboratory, whether in a state department of public health or university*".[26]

The FDA omitted any discussion of this potential significant legal limitation in their proposed rule and regulatory impact analysis, nor do they comment on whether the FDA nor HHS General Counsel accept or reject its own prior legal analysis. This concept, however, if upheld would have a profound effect on the impact (or lack thereof) on state-owned AMCs and other state-owned laboratory entities, and it should therefore be subject to more significant administrative or judicial consideration prior to advancing any proposed rules that may ultimately be found not applicable across a broad range of the industry. Conversely, if the FDA does now assert that it has the authority to regulate states and/or state-owned entities, then its conclusion in the proposed rule regarding Federalism (section XI) is factually inaccurate and a summary impact statement would be required.

Flawed Regulatory Impact Analysis

In conjunction with the proposed rule on LDTs, the FDA released its regulatory impact analysis.[27] This analysis, which is largely based on extrapolation of assumptions and outliers, contains significant and material errors and misrepresentations of the impact of the proposed rule on the economy, the clinical laboratory industry, and the performance of existing LDTs being used for patient care. This raises significant concern that the FDA either does not understand the

industry that it is proposing to regulate, or that it is neglecting to incorporate evidence from the community that does not support its assertions. Additionally, it is clear that the proposed rule would have major negative economic significance to the healthcare industry. We will outline several of our concerns with the regulatory impact analysis below.

Fundamental Error in the Analysis of Economic Benefits

The regulatory impact analysis ("Expected Reduction in Misdiagnosis", p38) incorporates significant and material misrepresentations of the number of IVDs that are offered as LDTs (estimated as 50%), referenced to a commercial market research report summary with no additional citation to source data. ARUP has, however, previously published real-world data regarding the percentage of test orders that are LDTs across our entire health system in 2021. Test orders is the relevant metric for their calculation of economic 'benefit'. Our data was made publicly available on a pre-print archive in December of 2022,[28] and it has subsequently been disseminated in the peer-reviewed literature and furthermore in a journal that the FDA references for other data.[29] Our ARUP data on test orders – which we believe are reasonably representative of U.S. health systems – demonstrate that LDTs are only a very small percentage of overall tests ordered by clinicians [3.9% of all test orders; with an additional 2.3% representing manual or standard (e.g., "pre-1976") assays].

Second, the regulatory impact analysis makes a significant and material error in its attribution of diagnostic error to the analytic phase of laboratory testing. For example, the FDA erroneously applies results in the Newman-Toker rate of diagnostic errors manuscript by inferring that 50% of diagnostic errors are attributable to laboratory tests.[30] The diagnostic literature, however, has consistently shown that most diagnostic errors are not the result of erroneous tests, but rather pre-analytic and post-analytic errors involving aspects of the diagnostic process beyond those which FDA could possibly regulate, and which would not be addressed by FDA's intended regulation. Common examples include a provider not ordering an indicated laboratory test, the failure of communication of test result to a member of the treatment team, or a specimen that was mislabeled outside the laboratory. It should also be emphasized that diagnosis includes multiple disciplines and technologies including information derived from outside the laboratory (e.g., radiology). Based on a more thorough assessment of the literature, we would estimate that approximately 1-4% of diagnostic errors may be attributable to faulty diagnostic test results.[31,32,33,34,35,36,3738] For the purpose of the reanalysis provided below, we will use the average of this range, thus 2.5%.

A reanalysis of the economic 'benefit' incorporating these two findings leads to a very different financial estimate of benefit to society. Recalculating the regulatory impact analysis Table 9 results with corrected multipliers from Table 8 to reflect a 3.9% probability of an LDT and a 2.5% probability that a diagnostic error was due to a faulty test result results in a Central Estimate Total Benefit (7% with Adjustment for Base Internalization) of $162M USD, as opposed to $39.5B as reported by the FDA. **We therefore believe that the FDA has made, at minimum, an approximately 250-fold overestimate in its assessment of financial benefit**. In their analysis, the FDA has failed to examine all relevant data and rather has used superficial assumptions that do not reflect clinical practice and represent a significant error in judgment. Additionally, the arbitrary

choice of unsupported evidence runs counter to more accurate information already available in the peer reviewed literature.

Furthermore, we vehemently reject the FDA's assertion that 47% of LDTs are 'problematic', and this is an additional multiplier in their calculation of economic 'benefit'. The FDA's position is based on an industry-sponsored study examining only one assay, and it is profoundly inconsistent with our own experience with LDTs, as demonstrated by excellent track record of LDT performance in our laboratory and comparable external proficiency testing performance for LDTs versus FDA tests in a retrospective analysis of our own performance. We believe that the FDA has made a significant and material error in their estimate, and that this additional 0.47 multiplier further is likely closer to zero. Additionally, the FDA also does not incorporate any factor to adjust for adverse events from FDA-cleared/approved assays – if one is replacing an LDT with an FDA-cleared/approved assay, the 'benefit' should be the avoidable cost related to the LDT minus the avoidable cost of the test that is used in its place. These updates essentially negate any purported financial benefit to society from the Table 9 estimates in the proposed rule.

Lastly, in circumstances where LDTs outperform FDA-cleared/approved assays (which is not uncommon in our experience), it is reasonable to conclude that the regulatory impact analysis may misclassify societal costs as benefits, as the LDT would actually decrease (rather than increase) the chance for diagnostic error. This analysis, however, is lacking in the regulatory impact analysis, further demonstrating that it is incomplete and erroneous.

Flawed Analysis of Economic Costs

The regulatory impact analysis also wrongly performs and yields significantly inaccurate and insufficient estimates regarding costs of the proposed rule. A notable error relates to the lack of any analysis regarding the reduction in access to safe testing. The regulatory impact analysis acknowledges this possibility but does not provide any impact analysis in this critical concern (page 87):

> *"Other unquantified social costs associated with this rule (or other manifestations of the costs that have been quantified) may include the impact on prices and access to diagnostics if many laboratories exit the market or discontinue offering certain IVD's rather than incur the costs of compliance with FDA requirement. There may be instances in which a laboratory may choose to exit the market or discontinue certain IVDs offered as LDTs due to compliance costs."*

The FDA's regulatory impact analysis did not assess how many laboratories would be forced to discontinue current testing due to compliance costs, and therefore it drastically minimizes the reduction in access to safe testing products due to the proposed rule. These compliance costs reflect not just registration and listing fees, but also the costs of updating processes for adverse event reporting, submitting tests for premarket review, and the costs associated with newly imposed manufacturer centric GMP and QSR requirements, all of which are underestimated by the FDA.

For LDTs with few competitor tests, discontinuation of testing in local settings also means prices will increase significantly due to lack of competition in the market. Additionally, any

remaining labs that can comply with the proposed rule will face significant costs associated with preparation of assay documents to meet FDA submission format and QSR requirements. This new FDA-imposed 'barrier to entry' for future tests in these markets also assures that testing will often become more expensive for new tests in the future. Unfortunately, the concepts of barrier to entry and the consolidation of testing to for-profit commercial laboratories and IVD manufacturer kits were also not analyzed in the FDA's regulatory impact analysis.

Finally, for LDTs withdrawn from the market due to compliance costs where no alternative tests are reasonably available, the costs to patients are even more troubling. Patients with rare diseases may not have timely access to essential diagnostics, and treatments may be delayed or not undertaken at all if a diagnosis cannot be made. Contrary to the FDA's assertion that commercial manufacturers will fill the gap, we contend that for many tests, including low volume testing, manufacturers will not expend the effort or resources for developing such tests as they will not be profitable. The proposed rule introduces a significant risk of harm to patients in such scenarios. Moreover, without any remaining tests to diagnose a disorder, physicians may have no other choice than to order more invasive procedures for diagnostic purposes, which will increase risk of adverse events and increase risk of litigation, both of which significantly escalate the cost of the rule beyond what FDA considered.

Incomplete Information

We are also concerned that in the proposed rule and the regulatory impact analysis, the FDA demonstrates a consistent bias of selective use of source data that supports its proposal, while neglecting and omitting – in entirety – extensive data from the peer reviewed literature that demonstrates outstanding performance of LDTs, as well as how they provide essential services for otherwise unmet needs. Additionally, the less restrictive and presently administered regulatory alternative – CLIA oversight – has not been extensively evaluated, particularly in settings where CLIA oversight supports the flexibility to meet local clinical needs and variations (e.g., test modifications for specimen type, specimen stability, collection tube requirements) that would otherwise be cost-prohibitive under FDA oversight. The FDA's regulatory impact analysis must reflect the full scope of how LDTs are used, including their clear advantages in practice guidelines and meeting current unmet clinical needs.

Increased Cost of Testing

The regulatory impact analysis also does not consider the full extent of the significant increase in cost of testing to healthcare facilities and patients that would result from enactment of the proposed rule. Compliance with the proposed rule would require user fees imposed upon clinical laboratories that offer LDTs – fees that would generate revenue for the FDA or third-party reviewers. These fees, however, in addition to the development and compliance costs cannot be supported by most clinical laboratories and would need to be passed on to the health system, insurance companies, and patients. This is particularly important given the prior and future cuts to reimbursement created by the Protecting Access to Medicare Act (PAMA).[39] The FDA rule therefore also has a direct impact to current and future Medicare and Medicaid patients that has not been considered.

COVID-19 Testing

The FDA's analysis also omits the benefits derived from the development of high quality COVID-19 testing by academic and public health laboratories early in the pandemic, and the FDA's own efforts to stifle such testing efforts prior to the announcement of the public health emergency in 2020.[40],[41] The LDT pathway – particularly in AMC settings – provides an essential and fundamental benefit to society during emerging public health threats. The FDA's proposed rule, however, would prohibit clinical laboratories from offering testing for emerging infectious diseases, chemical, or radiological threats prior to the formal federal declaration of a public health emergency and the activation of FD&C Section 564 EUA provisions. This would further delay, as opposed to encouraging, an effective and expedient national public health response. The regulatory impact analysis does not consider this substantial negative impact of the proposed rule on society.

FDA Responsibility under the Medical Device Amendments

Violation of the MDA General Rule

The "General Rule" section of the MDA [Sec. 519. (a)(1)] passed by Congress in 1976 specifically requires that regulations [underlines added]:

> "*shall not impose requirements unduly burdensome to a device manufacturer, importer, or distributor taking into account his cost of complying with such requirements and the need for the protection of the public health and the implementation of this Act*."[42]

The proposed rules are *unduly burdensome* (financially, administratively, and operationally) to the clinical laboratory community. As noted above and as outlined in the proposed rule, the *cost of complying* to the clinical laboratory community are extraordinary and undeniably underestimated. By ignoring the present value of a CLIA-oriented solution in clinical laboratory settings (particularly community hospitals and AMCs), the FDA and HHS have additionally failed to consider a less restrictive and easily administered pathway that currently works to provide outstanding care in our laboratories for patients. Additionally, the FDA has overstated risk to *public health* in its analysis, and it selectively chooses outlier evidence supportive of their assertions throughout the proposed rule and regulatory impact analysis while ignoring readily available literature and evidence to the contrary. Finally, the FDA fails to consider the severe challenges to the community if the proposed rule was finalized and attempted to be *implemented*. This will be described in the section below.

The Proposed Rule Cannot be Implemented by the FDA and Clinical Laboratories

One of the most significant concerns of the proposed rule is that it cannot be implemented by the FDA in its present form. This reality would cause tremendous disruption to clinical laboratory testing, and prolonged uncertainty to the broader healthcare community if implementation was attempted as described. The FDA simply does not have the staff to support a hundred or thousand-fold increase in regulatory submissions, nor is it likely that such professional expertise could be reasonably hired, and certainly without draining staff from clinical laboratories and the IVD community which would hinder ongoing innovation in those settings.

Historically, the 510(k) Third-Party Review Program[43] and 3P510k Third-Party Review Organizations have not been utilized much at all for IVD submissions,[44] largely due to manufacturer concerns for re-review by the FDA. Additionally, by regulation, the Third-Party Review Program cannot be used for PMA or de novo submissions, illustrating that the FDA under its own current policies cannot outsource a large portion of potential future submissions, for which it requires assistance.

In its proposed rule, the agency has not demonstrated that it understands the impact of what it is proposing, nor has it conveyed a plan to address the significant volume of submissions that would be received. Furthermore, the FDA does not analyze the impact of the inability of clinical laboratories to comply with applicable regulatory costs under the proposed rule. Additionally, as clinical laboratories have validated existing LDTs under CLIA requirements – and as FDA submission requirements will likely require administrative effort to adhere to newly-applied FDA format and QSR requirements – a significant and expensive community-wide effort will likely be required. The costs required and time necessary to complete this effort have also been omitted from the regulatory impact analysis.

The FDA has not considered the impact of the proposed rule on the existing IVD industry, given anticipated delays in regulatory reviews of future IVD submissions caused by the influx of clinical laboratory submissions of LDTs. The FDA was undeniably overwhelmed during the COVID-19 pandemic by a much smaller number of EUA submissions, leading to delays in regulatory reviews and preliminary consultations for conventional IVDs. This would be dramatically surpassed by a much larger influx of submissions of LDTs required by the proposed rule.

Finally, the regulatory framework under FDA's proposed rule exceeds the current capacity of the nation's laboratory workforce. Laboratories which have existing LDTs for which they intend to seek premarket approval under the proposed rule may not have the staff to undertake such an endeavor in a short timeline. Consequently, with staff shortage, many laboratories will have to select which of its clinically beneficial LDTs it can adequately bring to FDA for premarket approval. Most likely, laboratories will favor high-volume, common-disorder testing which generate more revenue, to the disfavor of lower-volume, rare disease assays. This dynamic will further exacerbate the rare-disease test shortage problem addressed in prior sections.

Practice of Medicine

The proposed rule also significantly hinders the practice of medicine for our physician medical directors. While the FDA mentions (section V.B.2.) existing MDA language regarding the ability of a practitioner to "prescribe or administer" devices, the perspective described in the MDA and presently by the FDA only reflects activities external to the laboratory. The MDA does not regulate medical activities *within* the laboratory, which are governed instead by practice of medicine as permitted by state medical practice acts and in alignment with federal CLIA regulations for laboratory operations. With existing CLIA oversight, pathology is already the most highly regulated medical specialty. Clinical and anatomic pathology, however, are also board-certified medical disciplines where medical judgment is used not just for test interpretation (i.e., sign-out), but also numerous within-lab activities including test development, medical guidance,

and judgment calls on what to do when a test does not meet the needs and expectations of our patients and clinicians.

The proposed rule would further restrict the ability of physician laboratory directors to use their medical judgment in such activities and by creating an undue financial and administrative burden on activities permissible and regulated under CLIA. This includes the drafting of test interpretive results and reference ranges to reflect the unique clinical needs of the patient populations that are served. The public benefits when patients and health care professionals receive expert scientific and medical guidance and publications on new testing methods, even if not yet reviewed by the FDA.

The proposed rule may also have First Amendment implications in this context, as well as conflicts with existing state medical practice acts. As an illustration, as an institution with medical providers in Utah, the Utah Medical Practice Act includes a definition of 'practice of medicine', including to [underlines added]

> "*(i) diagnose […] by any means or instrumentality*",[45]

and it further defines 'diagnosis' as

> "*(a) to examine in any manner […] to determine the source, nature, kinds, or extent of a disease*."[46]

Laboratory diagnostics clearly fall within the definition of practice of medicine in our state, and the practice of medicine extends beyond the narrow "prescribe or administer" construct as outlined in the MDA and by the FDA. We also believe that the conclusions in the proposed rule regarding Federalism (section XI) do not reflect the impact on practice of medicine given the conflict with our state medical practice act, as well as state programs that currently permit the review, approval, and use of LDTs (i.e., NYSDOH).

Test Modifications

The proposed rule also does not reflect the extensive administrative and economic burden placed on clinical laboratories for common test modifications that are currently routinely performed (and clinically necessary) for patient care across many, if not most, clinical laboratory settings.[47,48] A common test modification is for alternative specimen types sent to the laboratory by clinicians. Many IVD manufacturers only validate a limited number of specimen types to reduce development costs, whereas a laboratory may receive previously collected specimens from alternative source types or anatomical locations for which a provider is demanding a result. Laboratories currently perform body fluid validations under CLIA, and accrediting agencies also describe checklist requirements to support such testing.

As an AMC with a mission to share knowledge with the broader clinical community, ARUP has published numerous studies describing our experience and expertise with body fluid test validations.[49,50,51,52] Under the proposed rules, presumably any such activities would be considered a change in intended use and therefore subject to significant de novo submission fees. It is reasonable to conclude that clinical laboratories would not have resources for these submissions. Prohibition of such activities would also be unduly burdensome and a restriction on

the practice of laboratory medicine. It is also likely to reduce or eliminate the availability of this type of testing for patients.

Laboratories also frequently conduct validation studies under CLIA for additional phlebotomy tube types not specified in limited IVD package inserts. Additionally, it is not uncommon for laboratories to validate specimen stability under CLIA when required by laboratory operational processes. Alternatively, laboratories may even reduce stability limits when FDA package insert parameters are inaccurate and/or not supported by the laboratory's real-world validation studies.[53] Laboratories are also expected under CLIA to verify and/or validate reference intervals specific to their patient populations, even when they may differ from those provided in the IVD package insert. It is reasonable to conclude that clinical laboratories would not have resources for these submissions either.

The proposed rule also does not describe the legal and regulatory implications for modifications of existing IVD test kits on both the manufacturers and clinical laboratories. What is the legal responsibility and obligation of the original IVD manufacturer if it identifies that the FDA has cleared/approved a test (submitted by a clinical laboratory) that is based on a modification of its IVD kit? This is also not analyzed in the FDAs regulatory impact analysis. Currently the modified test (under CLIA) and the IVD manufactured (under FDA) are in separate regulatory domains, but under the proposed rule they would be combined under the single construct of manufacturing that does not currently or logically apply to a clinical laboratory setting or that may introduce additional liability implications and costs across the healthcare industry.

On this last issue, it should be emphasized that ARUP does not concur with the FDA's assertion that LDTs are 'manufacturing' activities, as LDTs are processes and services, and *not* mass-produced items sold to outside entities. It is clear from the proposed rule that the FDA has not considered the scope of locations where test modifications are occurring, nor has it incorporated this scope into its regulatory impact analysis demonstrating again that the cost analysis presents significant and material underestimates. The FDA has not examined all relevant data, and it has made an error in its assessment of the impact of the proposed rule on the clinical laboratory and broader healthcare communities. A less restrictive and easily administered alternative to test modifications (i.e., continued oversight under CLIA) has not been evaluated.

Lastly, the issue of test modifications is of financial significance to clinical laboratories, as instrumentation is often replaced when a vendor-lease term ends or when service and support costs justify replacement. This is often, but not always, within a five-to-eight-year time frame. Instrument replacement is often a time when a clinical laboratory considers alternative vendors. Under the proposed rule, it is our presumption that instrument replacement to new generations of platforms (or those from alternative manufacturers), would require new FDA submissions for all modified FDA-cleared/approved assays on those instruments, potentially as frequently as every five-to-eight years. This cost is also not included in the regulatory impact analysis.

Development of the Proposed Rule

When the United States Office of Management and Budget (OMB) received the FDA proposed rule on July 26, 2023, the FDA had classified the proposed rule as *not* Section 3(f)(1) significant.[54] This categorization is fundamentally inconsistent with Executive Order 12866[55] and as described in the April 6, 2023, memo from the Office of Information and Regulatory Affairs (OIRA).[56] Per the Executive Order, a proposed rule is 'significant' if, among other items, it adversely affects the economy, a sector of the economy, competition, public health, state, local, or tribal governments and communities, or underserved communities.

The proposed rule adversely impacts all of these listed categories, and by the FDA's own budget estimates, it dramatically exceeded the $200 million threshold for economic significance. Additionally, as noted above, the proposed rule raises numerous novel legal or policy issues that remain unresolved. While the proposed rule was subsequently re-assigned a categorization of Section 3(f)(1) 'significant' after OMB review, the FDAs own regulatory impact analysis demonstrated that their initial categorization was implausible. Such evidence further demonstrates a lack of consideration of all relevant factors by the FDA. More concerningly, it portrays a lack of partnership in helping to identify and establish a regulatory framework that could work for the industry being regulated. Again, a less restrictive and easily administered alternative to FDA oversight (i.e., continued oversight under CLIA) has not been thoroughly considered.

Academic Medical Centers

AMCs serve a vital role in patient care in the U.S. They serve as hubs for education, research, and innovation, as well as essential clinical care inspired by leading clinicians, scientists, and technologies. Additionally, AMCs are also institutions where specialty care is common and where patients may seek assistance with difficult diagnoses and complex clinical management and treatment. Given the history and prominence of pathology and laboratory medicine in these settings, LDTs are used by many AMC laboratories to meet the clinical needs of providers, clinical services, and patients.

The FDA acknowledges that its proposed rule would have unique implications on AMCs which operate diagnostic laboratories – and essentially all do. Furthermore, most, if not all, AMCs are non-profit organizations, and many are state-owned entities. Given this non-profit status and the current economic challenges faced by most health systems in the U.S., the compliance costs of the proposed rule would make the continuation of LDTs – and their future development and innovation in this setting – cost prohibitive in many, if not most circumstances. This would have a clear negative impact on public health and this sector of the economy.

The inability of the FDA to identify a common regulatory definition for AMCs reflects the fact that they have not previously been regulated in the manner being proposed. More simply put, FDA oversight of LDTs in AMC clinical laboratories has not previously existed, and it would likely provide negligible clinical benefit but significantly increased cost to health systems and patients.

Language describing proposed characteristics of AMCs has been presented in the proposed rule and include [underlines added]:

"*laboratory for which a certificate is in effect under CLIA and that meets the requirements under CLIA to perform tests of high-complexity; that is part of an accredited public or nonprofit private AMC that has a medical residency training program or fellowship program related to test development, application, and interpretation; and that is integrated into the direct medical care for a patient, including specimen collection, testing, interaction with the treating provider, and, as appropriate, patient treatment based on the test, all at the same physical location*."

The high-complexity CLIA certification is self-evident and an essential component of existing diagnostic testing in AMCs. We would also note that AMCs often are a unit of, or owned by, an accredited medical college or the parent university of the accredited medical college. AMCs may also contain basic science research laboratories that do not have CLIA-certification. Those laboratories should not (and legally cannot) perform clinical testing in the U.S.

The presence of training programs is also a common element of most AMCs, and the educational and clinical dynamic between trainees, laboratory directors, laboratory professionals, and clinicians is a differentiating element for this setting.

We also believe that the FDA's use of the term "direct medical care" is too limiting (if focused on the conventional concept of practice of medicine in the MDA) to reflect the breadth of care performed at AMCs. For example, all specimens are from patients and all clinical diagnostic testing is *direct* patient care. We do not believe that the FDA should consider or present clinical laboratory testing as any less direct of an activity as seeing the patient in an exam room. They are both essential medical services.

Proximity to providers is important, but we have found in our own AMC setting that we can also have valuable clinical interactions with clinicians and providers at a distance, both regionally and nationally. This has been successfully demonstrated over decades. Many AMCs approach telemedicine in a similar manner, with patients often being at a distance from the facility. An important element for clinical laboratory directors, laboratory professionals, and staff is to maintain working relationships with providers or referring laboratories, regardless of where they are located.

In this context, we disagree with the FDA's qualification regarding "all at the same physical location". In fact, many AMCs have centralized core laboratories where some testing is done in a centralized (often offsite) facility to conserve space within the hospital for other departments or clinical services. Thus, the "all at the same physical location" does not reflect the current reality in many AMC settings and should be removed from any definition of an AMC.

Finally, we do believe that other factors could be considered when defining and/or exempting AMCs. A history of continuous certification of compliance and accreditation with CLIA (e.g., 10 or 20 years) would demonstrate that the laboratory has a track record of quality operations. Additionally, a threshold number of LDTs previously developed could demonstrate a track record of successful development activities and expertise sufficient to ensure appropriate and ongoing patient safety.

We would therefore propose that a definition of AMC laboratory be limited to a:

"*laboratory for which a certificate is in effect under CLIA and that meets the requirements under CLIA to perform tests of high-complexity; that is part of an accredited public or nonprofit private AMC that has a medical residency training program or fellowship program related to test development, application, and interpretation."*

Small Business Fees

As most hospital clinical laboratories operate as part of a larger umbrella of a corporate health system, and as heath systems are increasingly being consolidated, it is unlikely many (if any) clinical laboratories would qualify for small business exemptions to reduced medical device user fees under the proposed rule.[57] It is important to consider this thoroughly in a regulatory impact analysis to understand the true financial impact to clinical laboratories and health systems.

Limitations of Distribution of Scientific Literature

We are also concerned about the FDA's assertion that clinical laboratories are manufacturers regarding the ability of laboratory scientists and physicians at AMCs to freely distribute scientific literature related to assays under their oversight, in accordance with restrictions under the FDA's existing 2014 *Guidance for Industry, Distributing Scientific and Medical Publications on Unapproved New Uses — Recommended Practices*.[58] We believe that the proposed rule may inadvertently impose restrictions on the academic and clinical community to freely communicate scientific and clinical information that is essential for the advancement of knowledge and provision of appropriate clinical care.

Training Programs

The negative impact of the proposed rule on training in AMC settings is also not considered by the FDA. If the cost of compliance is too great for ongoing LDT innovation and implementation in AMC settings, then our future trainees would no longer have exposure to these fundamental medical and laboratory activities. Elimination of LDTs from AMC settings therefore hinders the education of trainees and limits their exposure to test development and validation activities. It would also decrease their exposure to diverse technologies or test methods, including emerging technologies, and significantly impede their ability to develop clinical consultative and interpretive skills in laboratory medicine in relation to innovative technology and effective test utilization. This will negatively impact an already strained pipeline in clinical pathology and laboratory medicine, and it will be detrimental to patient care in AMCs and the populations that they serve. Lastly, it should be emphasized that the AMC laboratory training environment is an important pipeline of talent for IVD manufacturers and other entities involved with the clinical laboratory industry. It is likely that the negative impacts of an overly burdensome regulatory framework on training would be felt broadly in these other settings as well.

Labeling

Under the proposed rule, a CLIA-accredited laboratory would have to act simultaneously as both a laboratory and a manufacturer. We do not believe that clinical laboratories who develop LDTs are acting as manufacturers, as LDTs are not devices as defined by the MDA, thus the FDA's Sec. 820.3 (o) definition of manufacturer does not apply. We further anticipate significant problems for laboratories when adhering to guidance for manufacturers regarding labeling practices. For example, laboratories often publish a list of the tests they offer (i.e., the test menu), including both FDA-cleared/approved assays and LDTs. Information listed as part of this test menu cannot be subject to rigid labeling requirements and should not be considered 'promotional' – it typically provides essential information for clinicians to ensure appropriate specimen collection and handling that can be unique to the laboratory that is performing the testing. In general, laboratory websites cannot be considered advertising in the same way that manufacturers websites are, given that the laboratory provides services utilizing tests manufactured by outside parties.

LDTs also cannot reasonably be expected to adhere to the label requirements as noted in 21 CFR 809.10, as there is no physical container for which to adhere a label. Similarly, we anticipate other labeling requirements as noted in QSRs to be equally problematic and difficult to administer and/or comply with as they are not designed for the clinical laboratory setting. For example, creation of a package insert to meet the current labeling requirements does not make practical sense in a clinical laboratory setting. The purpose of the package insert is to provide instructions for use to someone other than the manufacturer. In the clinical laboratory setting, instructions like these are already part of its policy and procedure manual, the contents of which are regulated by accreditation agencies.[59]

Grandfathering

The concept of grandfathering existing tests has been a component of previously proposed regulatory frameworks and legislative proposals. Grandfathering was important in the implementation of CLIA requirements, and the FDA to some extent acknowledges the importance of this concept in its "pre-1976" construct. It is unclear why grandfathering is not included in the proposed rule, especially given that FDA has been amenable to it in the past. Grandfathering is critical to public health, because it would allow adequately performing testing to remain on the market where it may not otherwise be possible under the proposed rule due to compliance costs. Even given this, while grandfathering may alleviate some of the immediate damage to the clinical laboratory industry that the proposed rule would cause, it would not alleviate the long-term damage that would ultimately follow. Thus, we believe that grandfathering is an important concept to consider, but it is not sufficient to prevent the damage to industry and negative impact to patient care that implementation of the proposed rule would cause.

Software

We also anticipate significant problems for clinical laboratories when adhering to the guidance for manufacturers regarding the creation and use of software. Many tests, both FDA-cleared/approved assays and LDTs, involve simple calculations using the raw data that is produced by an instrument. For example, the optical density reading from a spectrophotometer

may be used to calculate an index value for an enzyme immunoassay. In the clinical laboratory setting, this calculation could be performed by software specific to the instrument, a validated Excel worksheet, interfacing software, middleware, or the laboratory information system (LIS). Some calculations (e.g., estimated glomerular filtration rate; eGFR) may even be calculated within an electronic health record (EHR) system in some healthcare facilities. In the case of an LDT, it would not be appropriate to consider the interface software or LIS to be elements of the test system that must be included in any premarket review.

Similarly, the clinical laboratory uses many electronic systems to maintain records that may be relevant to the validation of an LDT. It could be overly burdensome to meet the requirements of 21 CFR part 11 for systems that were designed to be used for clinical care, but under the proposed rule, would now also be used as the system of record for data that is included in a premarket submission.

Summary

It is our belief and concern for the public that if the FDA implements its proposed rule, essential testing services will become more difficult or impossible to access, particularly for patients with rare diseases, for underserved populations and those with less resources. 70% of today's medical decisions depend on laboratory test results.[60] For LDTs that remain on the market, there is a strong reason to believe that the price of such testing across the clinical laboratory community will rise significantly.

In the FDA's attempt to avoid the purported dangers of inaccurate LDTs, it has proposed a regulatory framework which will inadvertently result in more limited access to testing, higher prices, and potentially more harm to patients. Due to its inadequate consideration of economic, societal, public health, and clinical impacts – and an expansive position on claims regarding statutory authority – the FDA's proposal will likely not stand up to judicial scrutiny. This is particularly relevant given the 2022 U.S Supreme Court ruling on the major questions doctrine (*West Virginia v. Environmental Protection Agency*),[61] and the upcoming Supreme Court consideration of Chevron deference may create additional challenges to the FDA's approach next year.[62]

ARUP therefore urges the FDA to withdraw its proposed rule regarding LDTs. HHS should direct the FDA to work with CMS, legislators, and the broader clinical laboratory community – including the prioritization of meaningful and substantive bi-directional public forums – to assess how to better address LDT oversight without risking limiting patient access to safe LDTs, and in a manner which has an appropriate legal foundation.

Please feel free to contact us with any questions.

Sincerely,

Jonathan Genzen, MD, PhD
Chief Medical Officer, ARUP Laboratories

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