ARUP LABORATORIES

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

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March 19, 2024

The Honorable Brett Guthrie
Chairman
Subcommittee on Health
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
2322A Rayburn House Office Building
Washington, DC 20515

RE: Health Subcommittee Hearing on Regulation of Diagnostic Tests [March 21, 2024], Written Comment on Behalf of ARUP Laboratories from Jonathan Genzen, MD, PhD

Chairman Guthrie and Ranking Member Eshoo,

My name is Jonathan Genzen, and I am a clinical pathologist, a physician whose board-certified medical specialty involves the oversight and provision of clinical laboratory diagnostics for patient care. I serve as chief medical officer and senior director of government affairs at ARUP Laboratories, a nonprofit enterprise of the University of Utah's Department of Pathology, where I also hold an academic position as a clinical professor. I previously served as ARUP's chief operations officer during the COVID-19 pandemic. In these roles and in my other activities as a laboratory medical director and physician/scientist, I have developed a direct and systematic understanding of how clinical laboratory diagnostics impact public health. It is from this perspective that I would like to express my grave concerns regarding the negative impacts on public health and patient care of the FDA's proposed rule on laboratory-developed tests (LDTs).[1]

Clinical pathology is also commonly known as laboratory medicine, and indeed, medicine is practiced inside of clinical laboratories and in many facets of activities. As a CLIA director and a physician, I am legally and medically responsible for the development and operation of all clinical laboratory testing performed under my certificate. I hold this responsibility with profound respect and dedication to ensuring that our laboratory continuously provides outstanding clinical laboratory diagnostic services to our health system, our customer laboratories, and most importantly, to the patients who rely on us for safe and accurate testing.

ARUP Laboratories and LDTs

ARUP is the nation's largest nonprofit clinical reference laboratory, with customers representing more than 2,000 hospitals and medical centers across all 50 states. We perform laboratory diagnostic testing that impacts millions of people each year, and we provide clinical laboratory services for our academic medical center – University of Utah Health. With more than

[1] FDA Proposes Rule Aimed at Helping to Ensure Safety and Effectiveness of Laboratory Developed Tests. September 29, 2023. https://www.fda.gov/news-events/press-announcements/fda-proposes-rule-aimed-helping-ensure-safety-and-effectiveness-laboratory-developed-tests.

100 board-certified MD and PhD physicians and scientists who oversee clinical testing, ARUP provides laboratory services across all medical disciplines. Our ARUP Institute for Clinical and Experimental Pathology® has more than 60 research and development (R&D) scientists focused on test development, assay maintenance and enhancement, and research activities. Consistent with our academic mission and commitment to sharing knowledge with the clinical community, ARUP's medical directors and R&D scientists publish more than 130 peer-reviewed studies each year involving clinical laboratory diagnostics.

There are more than 3,000 different assays on ARUP's test menu. Of these, more than 1,000 are LDTs. As such, our ability to support clinical laboratory testing for patient care would be directly impacted by the FDA's proposed rule on LDTs. Our concerns with the proposed rule are outlined in detail in our November 28, 2023, public comment letter to the FDA.[2] I will summarize some of our concerns in the present written comments for this subcommittee hearing.

LDTs and the Benefits to Patient Care

As a physician, I am very concerned that the FDA, in its proposed rule and public statements, is promoting a decreased confidence in the quality of clinical laboratory services to the American public in order to enact LDT regulatory oversight. That portrayal is completely discordant with my own experiences in clinical laboratories and from interactions with truly incredible colleagues across the country. The community of more than 100,000 clinical laboratory professionals prides itself in a culture dedicated to patient care and continuous quality improvement, yet the FDA continues to convey a narrative to the public that many LDTs are unsafe, often using rarer, esoteric, multivariate genetic testing as anecdotal evidence of its concerns.

A study of all clinical laboratory orders within our academic health system over an entire year, however, demonstrates a very different view on the common utilization of LDTs by clinical providers.[3] For example, 93.9% of all test orders by clinicians during 2021 were for FDA-cleared/approved assays, while only 3.9% of orders were for LDTs. FDA statements regarding the proposed rule "leveling the playing field" do not accurately portray the current clinical laboratory testing market, which is dominated by FDA-cleared and approved assays when quantified by the relevant metric, which is clinical order frequency.[4]

Furthermore, the most frequently ordered LDTs are typically single analyte assays used for essential clinical care when no FDA-cleared/approved alternatives exist.[5] These are often low-volume tests (in terms of total order numbers) but spread out across many different types of LDT assays. It is the nature of this issue – low volume / high differentiation – that creates

[2] https://www.regulations.gov/comment/FDA-2023-N-2177-5561
[3] Rychert J, Schmidt RL, Genzen JR. Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System. *Am J Clin Pathol*. 2023 Sep 1;160(3):297-302.
[4] FDA proposes long-awaited LDT enforcement rule. September 29, 2023. *Regulatory Focus*. https://www.raps.org/news-and-articles/news-articles/2023/9/fda-proposes-long-awaited-ldt-enforcement-rule
[5] Rychert J, Schmidt RL, Genzen JR. Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System. *Am J Clin Pathol*. 2023 Sep 1;160(3):297-302.

unfavorable current market conditions for LDTs, and this is the true barrier to entry for in vitro diagnostic (IVD) manufacturers who cannot justify resources for test development and regulatory submissions if there is negligible financial return. Rather than solve this conundrum in support of patient care and diagnostic innovation, the proposed rule exacerbates the problem by dramatically increasing compliance costs for clinical laboratories and making many LDTs cost prohibitive for everyone. As noted in our recent clinical laboratory survey, only 3% of survey respondents reported having sufficient financial resources to support newly imposed FDA user fees.[6] If laboratories cannot support user fees, they cannot continue offering essential diagnostic services. In this context, I am particularly concerned about the negative impact of the proposed rule for diagnostic testing in cancer, pediatrics, and rare disorders.

Costs to Society and Patients

In its justification of the proposed rule last fall, the FDA also released a regulatory impact analysis.[7] As outlined extensively in our public comment letter, I believe that the FDA dramatically overestimated risks of LDTs, it ignored the clinical benefits of LDTs, and it did not evaluate the negative impact from loss of essential testing that the proposed rule would cause to public health. Furthermore, we have shown that the FDA made numerous significant material errors in dramatically overestimating the financial "benefits" of the proposed rule to society – a staggering 250-fold error – and it underestimated and overlooked many components of the true costs to patients and health systems. Additionally, the regulatory impact analysis did not evaluate how many laboratories would have to discontinue essential testing services due to increased compliance costs and user fees, which will likely be several million dollars each for many LDTs. The FDA also did not evaluate how many tests would be eliminated from the market and the associated negative impact to patients that would follow, nor the financial impact associated with corresponding increases in pricing due to consolidation and decreased market competition. I believe these errors and omissions are inconsistent with the intent of the Administrative Procedure Act, and that the FDA should not advance the final rule before working to better understand the true impact of the proposed rule on the American public.

Ultimately, it is our profound concern that the costs of the FDA proposed rule to most clinical laboratories would be prohibitive. Our recent survey of clinical laboratorians from across the country reinforces these concerns – 83.9% of clinical laboratorian respondents whose labs perform LDTs believe that their lab would be negatively impacted by the proposed rule, and a majority expect to remove tests from their menus if the proposed rule is finalized.[8] This would have a clear and lasting negative impact on clinical laboratories, hospitals, health systems, and patients.

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[6] Smith L, Carricaburu LA, Genzen, JR. The FDA's Proposed Rule on Laboratory-Developed Tests: Impacts on Clinical Laboratory Testing and Patient Care. https://www.medrxiv.org/content/10.1101/2024.02.28.24303459v2.

[7] Laboratory Developed Tests Regulatory Impact Analysis (Proposed Rule). https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/laboratory-developed-tests-regulatory-impact-analysis-proposed-rule.

[8] Smith L, Carricaburu LA, Genzen, JR. The FDA's Proposed Rule on Laboratory-Developed Tests: Impacts on Clinical Laboratory Testing and Patient Care. https://www.medrxiv.org/content/10.1101/2024.02.28.24303459v2.

LDTs and Responding to Public Health Threats

I am also extremely concerned about the negative consequences of the proposed rule on the ability of clinical laboratories to respond to future pandemics and public health threats. A consequence of the proposed rule is that it would prohibit LDT offerings for emerging threats prior to either FDA-clearance/approval through traditional slow pathways, or a formal declaration of a public health emergency and activation of the Food, Drug, and Cosmetic Act Section 564 emergency use authorization (EUA) provisions. This would delay national responses to emerging infectious diseases, as well as chemical and radiologic threats. Any LDT regulatory oversight proposals should encourage the use of clinical laboratory diagnostics to facilitate a rapid and effective national response, rather than hinder it.

LDTs and the Important Role of CLIA

Despite the January 18, 2024, joint letter from the FDA and CMS regarding LDTs,[9] as a physician, I strongly believe that CMS has an essential role to play in current and future LDT oversight, particularly in the context of test modifications, low and moderate-risk LDTs in CLIA high-complexity laboratories, facilitating LDT transparency, and collaboration with CLIA-deemed accreditation organizations. The Clinical Laboratory Improvement Advisory Committee (CLIAC) should be empowered to discuss LDT oversight in all its ongoing and future CLIA modernization efforts, as I believe that this is in the best interest of promoting public health. As examples, several external CLIA accreditation organizations already require evidence of clinical validity for LDTs, even though this requirement is not specifically outlined in CLIA performance standards. Another justification used for FDA oversight of LDTs has been the lack of sufficient information about the extent and numbers of LDTs currently in use. CMS could easily compile this information from CLIA applications and CLIA accreditation organizations, and this would provide greater visibility of existing LDTs for future oversight proposals and for the public.

Grandfathering Provisions

The FDA's proposed rule also does not contain any grandfathering provisions, which would enable existing LDTs to remain on the market despite a new regulatory structure. We support grandfathering provisions in any LDT oversight proposal, as they would help to ensure patient access to essential testing services. Grandfathering provisions, however, would only delay the negative impacts of the current proposed rule, but they would not eliminate the negative impacts long term. Clinical laboratories need ongoing flexibility to maintain and update LDTs under existing CLIA performance standard requirements without risking loss of grandfathered status. For example, equipment replacement, supply chain disruption, and automation requirements to meet changing test volume demands can impact existing LDTs. If laboratories cannot adapt to these disruptions, laboratory services will be delayed, and patients may be further harmed by the proposed rule.

[9] FDA and CMS: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made. January 18, 2024. https://www.fda.gov/medical-devices/medical-devices-news-and-events/fda-and-cms-americans-deserve-accurate-and-reliable-diagnostic-tests-wherever-they-are-made/.

Test Modifications

I would also like to emphasize the importance of keeping test modifications in high-complexity clinical laboratory settings under existing CLIA oversight and performance standards.[10] Test modifications are a relatively common (and beneficial) practice under CLIA to validate alternative specimen types received from clinicians, alternative specimen containers, specimen stability parameters, automation of manual processes, and to address to critical supply chain needs. Laboratories can currently perform these activities under CLIA validation requirements. The proposed rule, however, would introduce conflicting requirements, and laboratories could no longer adapt to health system needs without introducing significant additional compliance costs and delays in patient care. Again, under the proposed rule, most laboratories would be faced with discontinuing essential services in the context of test modifications that would become cost-prohibitive and/or delayed by new review requirements.

Practice of Medicine

I am also concerned that the FDA's proposed rule impinges upon the practice of medicine. The Medical Device Amendments does not authorize the FDA to regulate laboratory medicine activities. The proposed rule, however, would restrict the ability of physician laboratory directors to use their medical judgment, by locking down test interpretive comments in "labeling" requirements, for example, and by prohibiting test modification activities by physician laboratory directors outside of FDA review. Furthermore, the proposed rule conflicts with several state medical practice acts that include broad definitions of the practice of medicine and the act of diagnosis that are consistent with routine activities performed within the clinical laboratory by board-certified pathologists.[11] The FDA's proposed rule also raises significant First Amendment concerns regarding restrictions on what physicians could say regarding test interpretations or share in the form of scientific findings outside of FDA review. There are medical activities within the laboratory, and the proposed rule impinges upon these activities by licensed physicians.

Lack of Statutory Authority

It should be emphasized that we do not believe that the FDA has the statutory authority to regulate LDTs as medical devices. I have extensively researched the regulatory history of LDTs and have published numerous peer-reviewed articles in this topic.[12,13,14,15] LDTs are services, not products or physical devices. LDTs are not mentioned in the Medical Device Amendments of

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[10] 42 CFR 493.1253 - Standard: Establishment and verification of performance specifications.

[11] Utah Medical Practice Act. https://le.utah.gov/xcode/Title58/Chapter67/C58-67_1800010118000101.pdf.

[12] Genzen JR, Mohlman JS, Lynch JL, Squires MW, Weiss RL. Laboratory-Developed Tests: A Legislative and Regulatory Review. *Clin Chem*. 2017 Oct;63(10):1575-1584. https://pubmed.ncbi.nlm.nih.gov/28687634/.

[13] Genzen JR. Regulation of Laboratory-Developed Tests. *Am J Clin Pathol*. 2019 Jul 5;152(2):122-131. https://pubmed.ncbi.nlm.nih.gov/31242284/.

[14] Mohlman JS, Genzen JR, Weiss RL, Schmidt RL. Reliability and Validity of Proposed Risk Stratification Methods for Laboratory Developed Tests. *Lab Med*. 2019 Apr 8;50(2):194-201. https://pubmed.ncbi.nlm.nih.gov/30169875/.

[15] Rychert J, Delgado JC, Genzen JR. Modification of In Vitro Diagnostic Devices: Leveling the Playing Field. *Clin Chem*. 2020 Jun 1;66(6):760-762. https://pubmed.ncbi.nlm.nih.gov/32278318/.

1976 (MDA), nor were they discussed in Congressional hearings prior to its passage.[16] In fact, it wasn't until16 years after the enactment of the MDA that the FDA first acknowledged an awareness of the existence of LDTs.[17] LDTs are not commercially distributed through interstate commerce, and, concordantly, clinical laboratories have been specifically exempted from FDA registration for decades.[18] Prior analysis from HHS itself also asserts that the FDA's authority over IVDs does not likely extend to states and state-owned entities (e.g., state-owned university laboratories and public health laboratories as two prominent categories).[19] Finalization of the proposed rule is therefore in conflict with existing statutory authority.

Conclusion

In summary, my primary concern regarding the FDA's proposed rule on LDTs is that – in its effort to minimize the purported risk of "unsafe" LDTs – the proposed rule would eliminate access to many more existing safe and effective LDTs that are critical to ongoing patient care, but that are not financially sustainable under FDA user fees and compliance costs in hospital laboratory settings. What is equally troubling is that the FDA did not evaluate the negative public health impacts of the proposed rule. I am also concerned that increased costs caused by the proposed rule would contribute to further healthcare inequities between those able to afford and access such services and those who cannot.

As a board-certified pathologist, I strongly believe that the adverse public health consequences of discontinuing safe LDTs will vastly outweigh the purported benefits of the proposed rule, both in terms of patient safety and economic impact. For this reason, I ask that the FDA and HHS halt the advancement of the rule and work more closely with clinical laboratory stakeholders and CMS to devise a balanced regulatory framework that will not negatively impact public health or create further undue burden on the clinical laboratory community, hospitals, healthcare systems, and patients.

Sincerely,

Jonathan Genzen, MD, PhD
Chief Medical Officer and Senior Director of Government Affairs
ARUP Laboratories

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[16] Genzen JR, Mohlman JS, Lynch JL, Squires MW, Weiss RL. Laboratory-Developed Tests: A Legislative and Regulatory Review. *Clin Chem*. 2017 Oct;63(10):1575-1584. https://pubmed.ncbi.nlm.nih.gov/28687634/.

[17] Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation (Draft Compliance Policy Guide). Food and Drug Administration. Center for Devices and Radiological Health. Rockville, MD. August 3, 1992.

[18] 21 CFR 807.65, subpart i.

[19] Federal Authority to Regulate Laboratory Developed Tests. June 22, 2020. Robert Charrow, General Counsel. To Stephen Hahn, M.D., Commissioner of Foods and Drugs.