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April 2, 2024

The Honorable Bill Cassidy
455 Dirksen Senate Office Building
Washington, DC 20510

RE: Clinical Laboratory Diagnostics – Request for Information

Dear Senator Cassidy,

My name is Jonathan Genzen, and 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. ARUP is the nation's largest nonprofit clinical reference laboratory, with over 2,000 hospital customers across all 50 states. As such, our high-quality clinical laboratory testing impacts millions of patients each year.

I'd like to thank you for this opportunity to provide feedback on the regulatory framework for diagnostics under the FDA and CLIA. The responses to questions listed below were compiled from multiple individuals at ARUP representing several teams, including medical directorship, quality and compliance, and research and development. Given the breadth of questions, and to adhere to the April 3, 2024, RFI deadline, please consider these comments as preliminary thoughts across a wide range of issues regarding the FDA, CLIA, and clinical laboratory operations. We hope these responses prompt further discussion and consideration. Please contact me by email at jonathan.genzen@aruplab.com with any questions or if you would like to discuss these issues in more detail.

FDA REGULATORY FRAMEWORK FOR DIAGNOSTICS

1. How well is the FDA's medical device framework working for the regulation of diagnostic products? Are there improvements that should be made?

We suggest that the FDA's medical device framework – in its application to commercially distributed in vitro diagnostics (IVDs) – is effective but slow. This slowness (and the associated expense to developers) does hinder innovation in new IVDs, in favor of deference to a current framework that is dominated by comparisons to existing predicate devices rather than incentivizing improvements. New innovative devices – and even new claims and intended uses for existing devices – face significant compliance costs with user fees and regulatory submissions. While the existing

regulatory framework certainly helps to ensure the safety and effectiveness of devices, it also hinders assay improvements that could also benefit the public health. For example, there is no incentive – but rather direct financial cost – for IVD manufacturers to submit to the FDA assay improvements in support of standardization and harmonization efforts that are currently championed and funded by the CDC.[1] Rather, the current FDA regulatory framework in many ways prioritizes stability over improvement.

It is significant that the term product is listed in the question stem, as there is a history associated with this term that illustrates the FDA's efforts over time to increase its regulatory oversight beyond specific Congressional authorization. The FDA introduced the concept of 'in vitro diagnostic products' in 1973 through federal rulemaking, defining this term to include reagents, instruments, and *systems*.[2] The Medical Device Amendments of 1976 (MDA), however, defined devices to include *in vitro reagents* [or other similar or related articles], but the MDA itself did not include the term system within the statutory text.[3] The FDA, however, subsequently reintroduced this term into its IVD product definition,[4] and it uses the term "systems" in the preamble to its October 2023 proposed rule to justify a regulatory authority over LDTs.[5]

This is contrary to LDTs being services and not physical devices. LDTs were not discussed in Congressional hearings prior to the MDA's passage, and LDTs are not mentioned in the MDA statutory text itself. While the FDA has claimed that it has maintained a policy of "enforcement discretion" over LDTs since the passage of the MDA, this is not legally plausible as the FDA has also acknowledged that it was not even aware of the existence of LDTs until approximately 1992 – 16 years later.[6] We therefore believe that the FDA's current proposed rule on LDTs exceeds its statutory authority, and we have provided this feedback to the FDA in our previous public comment letter,[7] as well as in feedback from ARUP to the Office of Management and Budget.[8]

[1] Clinical Standardization Programs. Centers for Disease Control and Prevention. https://www.cdc.gov/labstandards/csp/index.html.
[2] 21 C.F.R. § 167 (1973).
[3] Public Law 94-295-May 28, 1976.
[4] https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-809.
[5] https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests.
[6] 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.
[7] https://www.regulations.gov/comment/FDA-2023-N-2177-5561.
[8] https://www.reginfo.gov/public/do/viewEO12866Meeting?viewRule=true&rin=0910-AI85&meetingId=333723&acronym=0910-HHS/FDA.

a. Of these specific changes, which would require Congressional action, and which can be effectuated by the FDA alone?

The adoption of a more practical, risk-based approach to IVD oversight would require Congressional action. Such action could create definitions of risk that are more directly applicable to IVDs. We will discuss the concept of risk in more detail throughout this RFI response. While risk-based definitions were discussed in the Verifying Accurate Leading-edge IVCT Development (VALID) Act [and prior discussion drafts], it is our ongoing concern that the VALID Act would also have a disastrous negative impact on essential LDT offerings, while simultaneously decreasing regulatory requirements for existing IVD manufacturers who distribute kits to external laboratories. None of this addresses the challenging financial landscape of offering LDTs for rare disorders when an otherwise commercial market for distributed IVD kits is not sustainable. Thus, we do not believe that the VALID Act is an appropriate regulatory framework for LDTs because it causes more problems than it solves.

The FDA could – through guidance and rulemaking – still enact practical improvements that could benefit IVD oversight. For example, allowing greater use of previously published studies on clinical validity, rather than requiring new studies, could increase public access to essential safe diagnostics. The FDA could publish templates of acceptable change-control plans that applicants could use to facilitate assay maintenance without creating an undue regulatory burden. If the proposed rule on LDTs is enacted, either the FDA or Congress will need to clarify how the nation will respond to future pandemic, chemical, and/or radiological threats in the absence of LDTs. Under the proposed rule, such LDT activities would be legally prohibited, and no clinical testing could be offered in the absence of an FDA-cleared/approved test or the formal declaration of a public health emergency and activation of FD&C Section 564 emergency use authorization (EUA) provisions. Again, such a delay could be catastrophic for public health.

2. Does the current device regulatory framework support the review of diagnostics that are developed using AI or that incorporate AI?

We believe that the current FDA device framework can support AI diagnostics, and, for example, it requires validation against data from multiple sites. The FDA's guidance on AI also allows for changes to AI systems after clearance if a change-control plan is in place at the time of validation and submission that details how systems will be reverified after model retraining. Easier ways to submit change-control plans post-hoc, and/or to enable the availability of generic change control plans that are acceptable to the FDA for common scenarios, could facilitate innovation in this rapidly changing field and for other IVDs.

Indeed, the use of AI in diagnostics is quickly evolving, and prior prescriptions on the number and types of cases that must be used for validations may become outdated as soon as they are published given the rapid development of new models – for example, the use of "few-shot learning" to fine-tune foundational models. Likewise, even internal validation methods are changing as new model architectures render the need for large datasets irrelevant, thereby democratizing the use of AI methods even in smaller laboratories. The FDA will need to dedicate significant attention toward keeping up with these advancements and understanding how public health can be both supported (as well as protected) by AI-based diagnostics. The Agency's commitment as outlined in "Artificial Intelligence and Medical Products: How CBER, CDER, CDRH, and OCP are Working Together," is a positive step toward supporting ongoing AI-based diagnostics,[9] and we are already seeing FDA-cleared solutions for specialties such as cytology hitting the market consistent with these efforts.[10]

3. What, if anything, makes diagnostics distinct among FDA-regulated medical products to warrant specific attention to how AI may be used in the review of product submissions?

We would suggest extreme caution prior to considering the use of any AI by the FDA to review actual product submissions. Scientific journals are asking comparable questions about AI-assisted peer review of manuscripts. However, the use of generative AI risks disclosing confidential information into external sources that compromises the privacy of submitted information and could make that information available for use by external sources without submitter consent. We are also concerned that as models are trained using pre-existing data, the potential use of AI in product submission reviews could simply perpetuate assessment according to predicate devices and paradoxically penalize innovation. At a more fundamental level, product submission review requires specialty-specific knowledge and expertise, and we are concerned that it could not be appropriately replicated using AI.

At a more practical level, however, it is possible that AI-assisted technologies could facilitate more timely clarification for nontechnical issues, such as application screening for "completeness," or for confirming that common errors (e.g., slight wording differences in intended-use statements across applications) are not occurring. If such

[9] https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device.

[10] https://investors.hologic.com/press-releases/press-release-details/2024/Hologic-Announces-First-and-Only-FDA-Cleared-Digital-Cytology-System--Genius-Digital-Diagnostics-System/default.aspx.

technologies were able to comply with privacy concerns and had an appropriate level of human oversight, we would also not want to deter the Agency from investigating opportunities to streamline the submission process. Robotic process automation, for example, is creating significant efficiencies across other industries, and the federal government should also work to achieve such efficiencies, where appropriate.[11]

4. Are the regulatory pathways intended to evaluate diagnostics for special populations (i.e., rare diseases or genetic disorders) working? a. How could they be enhanced to accelerate and authorize products for special populations, for example, certain companion diagnostics for rare biomarkers?

The regulatory approval process using current pathways for diagnostic tests used in patients with rare disorders contains numerous challenges and delays, which are exacerbated by challenging market conditions to support testing for rare disorders. We will describe two examples in this response to express our concerns: 1) heparin-induced thrombocytopenia (HIT), and 2) thrombotic thrombocytopenic purpura (TTP). Both HIT and TTP are disorders that may lead to life-threatening thrombotic ("blood clotting") complications if not rapidly diagnosed and treated.

HIT is caused by antibodies directed against a complex of heparin and platelet factor 4. These antibodies cause increased clearance and activation of platelets, with an overall prothrombotic phenotype derived from platelet activation. HIT is a "clinicopathologic" diagnosis, incorporating both clinical probability scores and laboratory tests. The causative anti-heparin-PF4 antibodies can be detected by immunoassays that have received FDA 510(k) clearance. However, these FDA-cleared immunoassays are used only as screening assays due to their high negative predictive value but low positive predictive value for HIT. Positive screening results must be confirmed with a functional assay. There are currently no FDA approved or cleared functional HIT assays; this is likely related to the increased complexity and lack of off-the-shelf assay components for functional HIT testing. Confirmatory HIT testing, such as the serotonin release assay (SRA), is essential for accurate diagnosis of HIT and for selection of appropriate therapy.[12] The major anticoagulants used in patients with confirmed HIT have increased cost and bleeding risk compared with unfractionated heparin; they are also more difficult to monitor with laboratory tests. Diagnosis and treatment selection for HIT involve complex clinical decisions that are dependent on LDTs.

[11] https://en.wikipedia.org/wiki/Robotic_process_automation.

[12] Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv: 2018;2(22):3360-3392.

The clinical syndrome of TTP was initially described in the 1920s.[13] Between 1996 and 2001, a von Willebrand factor cleaving metalloprotease, identified as ADAMTS13, was found to be decreased in TTP patients. This molecule cleaves large von Willebrand factor multimers into smaller multimers that are less likely to spontaneously bind platelets and therefore are less thrombogenic. The first ADAMTS13 activity assay (FRET) was developed and described in the literature in 2005; it was subsequently rapidly incorporated into clinical practice. An immunoassay was subsequently created, and both assays are currently used for clinical diagnosis. There are no FDA-approved versions of the FRET assay available. Until recently, there were also no FDA-approved immunoassays. The first ADAMTS13 activity immunoassay was finally approved through the FDA 513(f)(2) de novo pathway as a class II device on February 28, 2024.[14] If laboratories had waited to begin clinical testing for ADAMTS13 activity until an FDA-approved device was available, there would have been an additional 19-year delay in clinical use of laboratory tests for diagnosis of TTP. This example, while complex, is a great illustration of how the current regulatory framework is not supporting rare diseases well.

It is also important to note that the approval of one assay does not resolve the lack of access to FDA-cleared/approved methods. For TTP, only a single kit is approved, while other LDTs remain in routine clinical use to support patient care. Should ADAMTS13 activity only be performed by laboratories using the one approved assay? This strategy has the potential to significantly increase turnaround time for results, delaying diagnosis for a disorder that is potentially fatal. Additionally, in many cases, ADAMTS13 deficiency in TTP is due to acquired anti-ADAMTS13 antibodies (immune TTP). The assays used to detect anti-ADAMTS13 antibodies include a functional inhibitor assay (a modification of the activity test kit that is not specifically described in the package insert for the approved assay) as well as an immunoassay that quantitates anti-ADAMTS13 antibodies. Neither method for antibody detection is FDA-approved. In summary, although there has been slow progress on FDA approval of assays for TTP, there remains significant room for improvement in achieving timely assay approval and approval of a greater number of assays for this rare and potentially fatal disease.

These are just two examples of thousands of different rare diseases that are representative of the challenges of testing when FDA-cleared/approved assays are either unavailable and/or do not offer a sufficient financial incentive for an IVD manufacturer to develop such kits. This latter concern is exacerbated by FDA oversight proposals for LDTs, which do not "level the playing field" but rather make testing for rare diseases cost prohibitive.

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[13] Lammle B, Vanhoorelebeke K, Kremer Hoivinga JA, Knobl P. 100 years of thrombotic thrombocytopenic purpura: a story of death and life. Hamostaseologie. 2024;44(1):59-73.

[14] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?id=DEN230024.

5. Are there regulatory hurdles to expanding the settings in which diagnostics are performed, i.e. point-of-care (POC) tests performed in patients' homes? a. In what ways could/should FDA leverage regulatory flexibilities to reduce testing barriers?

While the rigor required for point-of-care (POC) testing regulation is, in our view, necessary, regulatory flexibilities could be considered for at-home, self-collection of certain, lower error-prone specimen types (e.g., saliva, urine, capillary blood) to be delivered to CLIA-accredited laboratories for testing. This is currently not possible for laboratories to offer without registering as a manufacturer with the FDA (or using FDA-cleared/approved collection kits from an external suppliers). The FDA could, for example, leverage regulatory flexibility by permitting CLIA laboratories to provide low-risk, validated POC collection kits directly to patients, if these kits follow standardized collection, transportation, and/or safety requirements that are predefined by the FDA. The lack of such general standardized requirements hindered home collection of many millions of specimens during the COVID-19 pandemic, unnecessarily exposing healthcare providers to infectious risk for collections that easily could have been completed at home.

Additionally, many states require that all laboratory testing be ordered by a licensed physician. Greater flexibility and state allowances for certain types of direct-access testing could allow CLIA-accredited laboratories to provide more tests directly to patients, who could receive straightforward and intuitive results directly. In the evolving world of personalized medicine, allowing patients to order certain tests, collect the specimens themselves, have them tested directly by a licensed laboratory, and receive the results directly to their personal devices is one way to help meet the demand for easier-to-access, and potentially lower cost healthcare. Understanding the risks, but also allowing for some flexibility in the existing regulatory landscape, could help meet this demand. We acknowledge that while this involves aspects of diagnostics outside the FDA's purview, undue regulatory burden on the assay and collection kit approval process also hinders such testing.

6. What are your views on FDA's implementation of predetermined change control plans; is FDA's approach in its recent guidance readily applicable to IVDs and other diagnostic products?

The rationale for the predetermined change control plans (PCCPs) can also be applied to IVDs. Given the FDA's stated intention to regulate LDTs and the existing restrictions on IVDs, PCCPs could provide additional flexibility for developers. The ability to identify less-critical / lower-risk components of tests – and allowing flexibility in the regulations to change and update these components without resubmitting a request to

the FDA – would increase a developer's ability to provide timely, high-quality test results. As noted above, we think there is an additional opportunity to expand the use of generic change control plans to allow for innovation in existing assays and in a way that would minimize the financial burden of making improvements. As proposed, we anticipate that the FDA may receive tens of thousands of PCCPs for review and approval if the LDT proposed rule is enacted. It is likely that many types of changes are common between IVDs. The FDA should work to simplify this process rather than roll out a system that inadvertently adds complexity and disrupts standardization.

We have also heard discussions regarding PCCPs and their potential application for addition of genetic variants to FDA-cleared/approved next-generation sequencing (NGS) panels, or, alternatively, of new analytes to toxicology screening tests and confirmatory panels. It would be essential for the FDA to clarify its position on whether these would be acceptable use practices for PCCPs, or whether addition of new analytes or variants would require resubmissions to the FDA. Without that clarity, it is difficult to ascertain the practical impact of PCCPs.

7. Does the FDA's current risk classification framework properly measure risk versus regulatory controls for diagnostics products? a. If not, how can FDA's risk-based regulatory approach to diagnostics be improved to better align the degree of regulatory oversight with patient risk and benefit?

The FDA's current approach to risk-based classification of diagnostics relies primarily on device classification to assign risk and on the application of the corresponding level of regulatory control. The device class (i.e., class I, II, or III) functionally defines the regulatory controls deemed applicable, but this approach does not actually align well in terms of balancing the benefit and risk in patients. The level of premarket review that follows from this approach is overly burdensome and presents a barrier to the availability of high-quality diagnostic testing for clinical use by ordering providers.

For example, in most instances, analytical methods underlying laboratory tests are well-established in science, clinical practice, and medical literature. This fact is unaccounted for in the FDA's current approach to risk-based consideration of diagnostics. An improvement to the FDA's approach might be to allow high quality diagnostic testing providers (e.g., high-complexity CLIA laboratories using LDTs) to be approved for *methodological categories* of IVD design and use, as opposed to requiring premarket approval or 510(k) submission on an individual test-by-test basis. This concept is generally aligned with the framework of *technology certification* included in an earlier draft of the VALID Act, but it was unfortunately limited to only low- and medium-

risk tests. Because the FDA generally considers new tests as "high risk" (even when those new tests do not present a substantial risk medically), we are still concerned that the technology certification program would not fully address the overwhelming compliance costs associated with FDA oversight of LDTs. It is, however, a welcome addition to oversight proposals.

We should also note that while discussion of risk classification is important, what is even more important is how the agency classifies tests according to those risk categories, as classification can be extremely subjective. We have previously conducted and published a risk-stratification exercise to illustrate the practical challenges when applying risk categories to laboratory tests.[15] It is our strong recommendation that the agency and/or legislators conduct similar risk-stratification exercises for common types of tests – and they should share the results with the public – prior to advancing new frameworks for risk classification of laboratory tests in oversight proposals.

8. In considering reforms to FDA's risk classification framework for diagnostics, what types of IVDs should be exempt from premarket review?

The FDA's risk-classification framework does not sufficiently provide detailed guidance for laboratories to definitively understand and define whether there is a predicate device for an IVD or LDT. The FDA databases are generally cumbersome, siloed, and convey an inconsistent application of classification product codes and device-classification names that do not always align with a predicate specimen source type or assay methodology. This uncertainty will make it exceedingly challenging to determine whether there are true pre-existing devices and/or whether a test is exempt from premarket review. Clearer guidance for determining the FDA's position on predicate devices for LDTs would be critical, and we suggest that this must be completed by the FDA prior to rolling out any final rule or associated timelines. Otherwise, it will be challenging (if not impossible) for many clinical laboratories to comply.

Exemptions to premarket review, and points to consider when determining risk, could include: 1) a test that is validated using alternative reagents with the same matrix or using alternate consumables, 2) a process that is automated while still following step-by-step guidance in the predicate device's package insert for manual operation, 3) validating extended (or reduced) stability requirements on an approved test, and 4) modification of an FDA-cleared/approved assay to account for additional source types requested by clinicians (e.g., body fluids). IVDs that are currently in use and that have

[15] 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/.

been validated by laboratories, but that do not provide a result that will be used as a sole indicator for clinical decisions, should also be considered exempt from premarket review.

a. What factors related to risk management should be applied to risk classification of IVDs?

Several professional organizations have already drafted potential risk-classification frameworks for IVDs and/or LDTs. We would direct the reader to the Association for Molecular Pathology's 2015 CLIA modernization proposal,[16] as well as the 2020 position statement from the Association for Diagnostics and Laboratory Medicine (formerly named the American Association for Clinical Chemistry),[17] as two examples of frameworks for risk classification that more closely align with how LDTs are used than the existing FDA device classification structure. As noted above, risk-stratification exercises are essential to ensure that classification structures work as intended, and to assess the potential regulatory and compliance burden that such structures will place on federal agencies, IVD manufacturers, and the clinical laboratory community.

9. Is the "safety and effectiveness" standard against which diagnostics are reviewed the most appropriate review standard to assign risk management for clinical tests?

The "safety and effectiveness" standard was designed with physical medical devices in mind (e.g., catheters, pacemakers, and surgical tools). While it provides a framework that has been adapted for use in IVDs, the FDA's focus on new clinical studies for premarket approvals – versus citing existing published research for a given analyte – increases the cost of PMAs significantly and therefore limits innovation in new diagnostics. It is also important to note that the safety and effectiveness standard only applies to premarket authorizations (high-risk/new). Premarket reviews (moderate-risk) are judged based on "substantial equivalence," which also does not incentivize or promote innovation or assay improvement.

If the safety and effectiveness standard is maintained, the FDA should consider ways to further refine how it is applied, so as not to perpetuate a hindrance on assay innovation. Put more succinctly, it is not surprising that most assay innovation is occurring with LDTs and not FDA-cleared/approved devices. The safety and

[16] Proposal for Modernization of CLIA Regulations for Laboratory Developed Testing Procedures (LDPs). Association for Molecular Pathology. https://www.amp.org/advocacy/documents/AMPCLIAmodernizationproposalFINAL8.14.15.pdf

[17] Oversight of Laboratory Developed Tests. Association for Diagnostics and Laboratory Medicine. October 1, 2020. https://www.myadlm.org/advocacy-and-outreach/position-statements/2020/oversight-of-laboratory-developed-tests.

effectiveness standard also does not factor in the use (and misuse) of clinical tests by ordering providers. Rather, it places the responsibility for safety and effectiveness on the developers alone from a product standpoint. For IVDs and LDTs, the safety and effectiveness of a test often relates more to how the test is used, given that the FDA and Centers for Medicare and Medicaid Services (CMS) both have strict analytical validation requirements that are already in place. This concept, however, is not factored into the FDA's existing regulatory framework or the proposed rule on LDTs.

10. Do the proposed reforms to FDA's device framework warrant the establishment of a new regulatory pathway specific to diagnostics? If yes, what are the principles that should guide such a new framework, as it would be applied to diagnostics currently subject to FDA premarket review?

It is our opinion that regulatory oversight of LDTs works well under the existing CLIA framework, and that improvements could easily be incorporated through CLIA modernization, if CMS allows these updates as part of its CLIA modernization discussions. Additionally, this would be a less restrictive and more easily administered method of LDT oversight than what the FDA rule or the VALID Act are proposing.

If the FDA continues to pursue oversight over LDTs, we believe that the existing device framework is wholly inadequate for diagnostics, and that a new regulatory framework should be considered. However, the VALID Act – while easing regulatory requirements for existing IVD manufacturers – would still be cost prohibitive for LDTs performed in clinical laboratories. As such, the VALID Act is just as damaging for patient care as the FDA's proposed rule. Therefore, we do not support its advancement.

Because our own research has demonstrated that nearly 95% of tests ordered by clinicians are FDA-cleared/approved assays (only approximately 4% are LDTs),[18] it is important to recognize that the VALID Act is more of an *IVD reform* proposal for manufacturers, that also happens to limit access to clinically essential LDTs. We therefore urge caution in framing the VALID Act as primarily an "LDT oversight" proposal in future hearings or discussions, because that framework does not represent the entirety of implications to the broader community.

Taking a further step back, the focus of recent diagnostic oversight proposals has been misdirected. The goal should not be the regulations themselves (e.g., "the same oversight structure in all settings"). Rather, the goal should be the availability of safe and effective testing to support patient care, regardless of setting. We can accomplish that

[18] 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.

goal through a more nuanced and tailored approach to different settings, taking the best aspects of FDA and CLIA oversight, rather than ignoring the value that CLIA has regarding LDTs. Different frameworks are appropriate for commercially distributed IVDs and LDTs performed in CLIA laboratory settings. This is why we believe it is essential to discuss CLIA modernization (including CLIA oversight of LDTs) as one of the options for future oversight proposals, because this is in the best interest of public health. We will discuss these concepts in more detail in the section on CLIA below.

CLIA REGULATORY FRAMEWORK FOR LDTs

1. What updates to the clinical laboratory regulatory structure under CLIA should Congress consider to reflect the latest scientific practices and safety standards?

We believe that there are opportunities to update CLIA regulations to incorporate several modern scientific practices and safety standards. For example, regarding LDTs, while CLIA does not specifically require documentation of references or studies in support of clinical validity, it is essential to note that several CLIA-deemed accreditation agencies do (e.g., CAP[19] and NYDOH[20]). In this context, CLIA regulations could be updated to account for what its accreditation organizations are already requiring. It is important, however, to acknowledge that these requirements should not impinge upon freedom of speech of medical providers, as will be discussed below.

Many clinical laboratories have also adopted quality management systems (QMS) under ISO 15189 or similar frameworks. Additional external accreditation, however, adds compliance costs to clinical laboratories and ultimately costs to patients. Therefore, greater incorporation of QMS best practices within CLIA itself could help negate the need for these additional expenses. As examples, CLIA could benefit from additional clarification regarding "change control," particularly in relation to document control and supplier qualification processes.

CLIA could also benefit tremendously by codifying the enforcement discretion related to remote work. Currently, only through continued enforcement discretion post pandemic, laboratories are permitted to allow review of digital images and data by licensed/trained professionals at offsite locations. This is an area where technological advances – and even employee expectations – are starting to diverge from CMS/FDA models that consider "physical location" of the licensed or registered establishment to be the site where all activity must occur, even when those activities are digital and can

[19] College of American Pathologists Laboratory Accreditation Program. Checklist Item COM.40625.
[20] Test Approval. New York State Department of Health. Clinical Laboratory Evaluation Program. Risk Attestation Form.

easily be conducted remotely. CLIA also does not have an adequate construct to reflect digital information and analysis that does not require a physical, traditional laboratory space when no "wet testing" is being performed.

Another key issue is that CLIA should also be modernized to reflect remote laboratory locations that are part of larger systems (e.g., to adopt a "hub-and-spoke" model for licensure that reflects the way that many complex laboratory operations now are organized). For example, clarification could be provided of where proficiency testing (PT) can be performed when multiple locations perform testing in a hub-and-spoke model, or when separate steps of the same testing process are performed at distinct locations. Rather than having a unique PT program for each location (under a separate license), would it be possible for PT to better mirror the workflow of patient specimens moving across a complex organization without undue risk of accidental PT referral?

We also believe that CLIA should serve a key role in clarifying how many LDTs are currently in use in clinical laboratories across the country. We have discussed this in a prior publication,[21] in our November 2023 public comment letter to the FDA,[22] and our March 2024 written statement the House Energy and Commerce Committee Subcommittee on Health.[23] As described in our public comment letter and re-presented below, CMS already collects information about assay manufacturers in CLIA permit application forms.[24] Additionally, CAP accredited laboratories already maintain a list of all LDTs performed within their laboratories,[25] and laboratories accredited by NYSDOH must submit LDTs for review and approval prior to their use in the laboratory.[26] The data for LDTs in use in the U.S. already exists and could be easily obtained with minimal draft guidance under CLIA. FDA oversight is not required to obtain this information for the American public.

2. What are your views on the effectiveness and use of the Clinical Laboratory Improvement Advisory Committee (CLIAC) in providing scientific and technical guidance to inform potential updates to CLIA standards?

[21] 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.
[22] https://www.regulations.gov/comment/FDA-2023-N-2177-5561.
[23] https://energycommerce.house.gov/events/health-subcommittee-hearing-evaluating-approaches-to-diagnostic-test-regulation-and-the-impact-of-the-fda-s-proposed-rule.
[24] Department of Health and Human Services, Centers for Medicare & Medicaid Services. Clinical Laboratory Improvement Amendments (CLIA) application for certification. CMS form 116. https://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/CMS-Forms-Items/CMS012169.
[25] Laboratory Accreditation Program. Checklist Item COM.40830 Test List—Modified FDA-Cleared/Approved Tests and LDTs. https://www.cap.org/laboratory-improvement/accreditation/accreditation-checklists.
[26] Test Approval. New York State Department of Health. Clinical Laboratory Evaluation Program. https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval.

We believe that CLIAC has an essential role in providing scientific and technical guidance, although its impact could be significantly improved through several changes. CLIAC is good at gathering information and perspectives from laboratories and compiling this information in reports including recommendations. CLIAC has a membership that represents broad points of view and expertise, enabling appropriate discussion regarding key issues. CLIAC is good at identifying areas of CLIA that need improvement and updating, and it has been effective at forming workgroups with expertise relevant to specific matters and the ability to form well-reasoned, written recommendations that incorporate workgroup perspectives. CLIAC's recommendations are generally clear and well-structured to "theoretically" guide CMS in taking relevant actions to update CLIA technical standards. CLIAC has been moderately successful in guiding a few recent changes by CMS, such as updating education requirements for laboratorians who perform nontraditional functions (e.g., histotechnologists) and decision-making relating to remote review of digital information/images following the global pandemic, although this is still only permitted under the framework of enforcement discretion.

As an advisory committee, CLIAC does not have any authority to implement recommendations, and the weight/impact of CLIAC recommendations appears to be limited. The impact of CLIAC (and corresponding working group) recommendations on Health and Human Services (HHS) and CMS are also likely hindered by highly structured modes of communication. Written recommendations are often limited to just a few sentences, and there is often no direct communication or interchange apparent between entities. The biannual public meeting schedules limit CLIAC's ability to handle more than a few key issues at a time. Thus, while CLIAC is fulfilling its advisory responsibility "on paper," it is unclear how often this important feedback from the community is considered and acted upon by the agency.

Specific to LDTs, we are concerned that the agenda-setting process of CLIAC – largely influenced by the agencies – may be hindering the ability of CLIAC to openly discuss LDTs as part of its CLIA modernization initiatives. It is important that advisory committees operate with independent judgement, consistent with requirements in the Federal Advisory Committee Act.[27] This is particularly concerning given the recent public statement cosigned by CMS arguing that CLIA should not be involved in LDT oversight.[28] We are skeptical that sentiment is also shared by CLIAC membership; open discussion within CLIAC could clarify this point for the American public and could better inform future HHS, FDA, and CMS proposals and statements on this matter.

[27] https://uslaw.link/citation/us-law/public/92/463

[28] FDA and CMS Statement: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made. January 18, 2024. https://www.cms.gov/newsroom/press-releases/fda-and-cms-statement-americans-deserve-accurate-and-reliable-diagnostic-tests-wherever-they-are.

3. Do the proficiency testing programs currently approved by the Department of Health and Human Services (HHS) reflect the latest clinical standards of laboratory medicine? Are there specialties, subspecialties, or analytes that should receive greater consideration for HHS approval?

Along with many clinical laboratories, we are acutely concerned with the increasing costs of proficiency testing (PT) products and programs. We therefore request that HHS factor in cost of compliance if it considers future changes and/or enhancements to PT programs. More specific comments on PT are included below.

As you may be aware, CMS recently updated the acceptance limits for specific analytes to reflect percentages (not standard deviation-based grading), and to include the addition of 29 regulated analytes to Subpart I. We believe this is the first time since 1992 that these specific regulations have been updated. With new testing advancements, we recommend this type of review be conducted more frequently than every 20 to 30 years and that greater public feedback be incorporated when these new changes are proposed. For example, CMS did not incorporate several important concerns regarding these changes, including: 1) the negative impact of percentage-based grading on low-concentration PT specimens, 2) clinically disadvantageous thresholds for hemoglobin A1c that are actually much looser than assay quality goals that IVD manufacturers are already able to achieve, and 3) paradoxical grading for already outdated cardiac troponin assays, even though high-sensitivity assays are already standard of care both in the U.S. and internationally. On this last point, the regulated analyte requirements are already clinically outdated before their implementation. CMS should be more proactive in reflecting the current state of clinical laboratory practice supporting patient care.

CMS could also provide more governance over its CLIA accreditation organizations and approved proficiency testing providers. For example, since the COVID-19 pandemic, we have experienced a general decline in PT surveys being shipped on schedule, forcing the laboratory to sometimes perform internal assessments to meet semiannual requirements. Information regarding limited number of participants in a survey should be provided by CLIA approved PT providers up front, so the clinical laboratories do not incur additional costs for surveys that cannot ultimately be used to fully evaluate their testing.

In general, we believe the CLIA approved PT providers offer services that reflect the clinical standards of laboratory medicine. Due to the recent changes in CLIA, with the additions and removals of regulated analytes and modifications to grading criteria

effective in January 2025, we will see if the PT providers are able to provide appropriate products that adequately reflect these updated criteria. At least one PT provider is already providing information about upcoming changes from CLIA in its participant summaries this year.

Regarding specialties/subspecialties covered under CLIA, it is still glaringly apparent that no molecular specialty or subspecialty are included, despite the incredible growth in this discipline in the past two decades. This is one area where CLIA regulations must be updated to reflect modern laboratory medicine. A CLIA accreditation organization (CAP) has already created a discipline for molecular pathology with its accreditation program, and it has created the following subdisciplines that require specialty inspectors for areas not covered by CLIA: 1) HLA (Human Leukocyte Antigen) NGS, 2) Infectious Disease NGS, 3) Inherited Genetics, 4) Molecular Oncology - Hematologic Diseases, and 5) Molecular Oncology - Solid Tumor. To adequately assess laboratories directly accredited by CLIA, CMS will need to either employ or contract with individuals with similar specialized training.

4. How well does the existing enforcement structure under CLIA work in ensuring compliance with regulatory requirements and taking action against noncompliance? What should be improved, if anything at all?

ARUP Laboratories believes that the existing CLIA framework for enforcement works well to help ensure compliance with regulatory requirements and take action against noncompliance. Examples include the requirement that all tests (including LDTs) undergo PT, where samples are sent to enrolled laboratories by an accredited vendor and results are then compared across laboratories or to predefined accuracy-based goals (when appliable). Under these programs, if a laboratory fails a PT event, the issue must be investigated and remedied to remain in compliance under CLIA. The inability to pass PT challenges can result in a laboratory not being permitted to perform such testing, and this helps to protect the public. PT is a real-world way of ensuring that testing methodologies from both FDA-cleared/approved tests and LDTs are functioning properly.

CLIA also requires laboratory inspections, performed by CLIA accreditation organizations (such as CAP and NYDOH), and sometimes performed by CMS/ local CLIA offices themselves. If issues arise with testing that could adversely impact patient care, consequences include fines, directed plans of correction, and other corrective actions. There are also self-reporting requirements for noncompliance that further reinforce laboratory safety and accountability from accreditation organizations and CMS.

As such, we believe the existing enforcement structure is adequate for ensuring compliance with regulatory requirements. The 2016 CMS inspection of Theranos is a profound example of how CMS successfully identified nonconformances and protected the public.[29] To the contrary, the FDA's 510(k) process cleared a medical device from the same organization whose leaders were ultimately convicted of fraud.[30,31] We state this difficult but important distinction to emphasize the critical role that CMS and CLIA should continue to play in the oversight of clinical laboratory diagnostics and LDTs.

Finally, it is also important to note that there still seems to be a disproportionate focus and penalty from CLIA on accidental PT referral, as well as the potential for inconsistent enforcement across different CLIA regions. Penalties should be directed toward intentional PT referral, and not accidental referrals that occur solely due to a specimen being treated like an actual patient when reflex algorithms would otherwise direct a true patient specimen to a different laboratory section or location. Guidance from CMS acknowledges this challenge for laboratories, stating both that "PT samples must be tested in the same manner you test patient specimens," as well as, "never send PT samples out of your laboratory for any reason, even if you routinely send out patient specimens for additional testing."[32]

5. Should legislative reforms address CLIA's quality system requirements? If yes, which of those changes would require Congressional action, and which could be effectuated by CMS alone?

In addition to recommendations listed above, we also recommend better aligning CLIA Subpart K with total quality management principles, including guidance on corrective and preventive actions and management of general processes that are not directly in the path of testing. We believe that restructuring the guidance could be effectuated by CMS alone and therefore Congressional action should not be required. Regarding LDTs, if CMS is not proactive in enhancing (rather than abdicating)[33] its

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[29] Federal inspection report reveals major problems at Theranos lab. *BioPharma Dive*. April 1, 2016. https://www.biopharmadive.com/news/federal-inspection-report-reveals-major-problems-at-theranos-lab/416680/

[30] Controversial multibillion-dollar health startup Theranos just got a huge seal of approval from the US government. *Business Insider*. July 2, 2015. https://www.businessinsider.com/theranos-gets-fda-approval-2015-7.

[31] Theranos founder Elizabeth Holmes reports to prison for defrauding investors. *ABC News*. May 30, 2023. https://abcnews.go.com/Business/theranos-founder-elizabeth-holmes-reports-prison-defrauding-investors/story?id=99626509.

[32] CLIA Proficiency Testing and PT Referral Booklet. https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/cliabrochure8.pdf.

[33] FDA and CMS Statement: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made. January 18, 2024. https://www.cms.gov/newsroom/press-releases/fda-and-cms-statement-americans-deserve-accurate-and-reliable-diagnostic-tests-wherever-they-are.

oversight responsibility over LDTs, Congressional action could certainly be beneficial and in the best interest of public health.

6. Where does redundancy exist, if at all, within the current CLIA regulatory structure with respect to accreditation standards under federal and state licensure programs, as well as through CMS-approved accreditation organizations?

Redundancy exists across most aspects of CLIA and CMS-approved accreditation organizations, and often by design. The existing practice of deemed status creates necessary redundancy to enable laboratories to meet each agency's/program's requirements, while still standardizing processes and remaining efficient. CLIA accreditation organizations update their standards regularly, while remaining in baseline alignment with CLIA. This provides more specific, updated guidance to better match evolving practices in laboratories, whereas CLIA is often slow to reflect these changes.

Requirements from state agencies (e.g., New York and California) are not fully aligned with CLIA regulatory structure or the requirements of other CMS approved CLIA accreditation organizations. This introduces logistical challenges and increased costs for laboratories that need to comply with requirements from multiple agencies and CLIA accreditation organizations to support the geographic scope from where patients are located.

Specific examples include:

- New York "Sole Assistant Director" and "Certificate of Qualification" holder requirement vs. CLIA "Laboratory Director" and director-delegated tasks do not fully align. These conflicting requirements complicate the development of streamlined policies and procedures that can withstand scrutiny of inspections across differing agencies.
- Education requirements for testing personnel vary across state agencies and CLIA, making it difficult to design a logical approach to staffing and hiring. Excess requirements paradoxically make it more difficult to hire qualified individuals and support patient care in certain testing areas (e.g., histotechnology).

7. In considering legislative reforms to CLIA, should LDTs be defined in statute? What aspects of test development would characterize such a definition?

To our knowledge, there are currently no legal definitions of LDTs in either federal statutes or existing federal regulations. LDTs are indirectly referenced in a CLIA performance standard – "modifies an FDA-cleared or approved test system, or

introduces a test system not subject to FDA clearance or approval (including methods developed in-house)."[34] The FDA's proposed rule on LDTs also does not attempt to create a definition for LDTs, but rather it attempts to exercise oversight by expanding the scope of where "manufacturing" of IVDs is performed to state, "including when the manufacturer of the IVD is a laboratory."[35] We believe this is another example of the FDA seeking to expand its oversight authority while sidestepping the original intent of the MDA.

Regarding the question of LDT definition, we do believe that establishing an appropriate definition may help differentiate high-risk LDTs (that could benefit from additional requirements) from lower risk LDTs (requiring minimal changes to current practices). We do not believe, however, that this definition should be within the FDA device framework, as LDTs are not medical devices but rather testing services. Additionally, any definition of LDTs should not incorporate terms such as "manufacturing," because clinical laboratories do not manufacture test kits for commercial distribution. Ultimately, we believe a definition for LDTs should fall within the framework of CLIA, not the FDA.

As noted earlier in our response, we also believe that a definition of LDTs could certainly incorporate various concepts of risk. For example, laboratory modification of an FDA-cleared/approved test for the purposes of including an alternative sample type or collection device, or for making another change that does not significantly alter the test system (such as automation), while still using the test for the same clinical purpose, is a low-risk endeavor and should not be subject to excessive regulatory burden. These tests would continue to be subject to development and validation requirements for analytical validity as they currently apply to LDTs under CLIA (i.e., accuracy, precision, analytical sensitivity, specificity, and reportable range). This process is working well and would not benefit from FDA oversight.

While laboratory results are interpreted in the context of clinical presentation and other diagnostic information (e.g., radiologic imaging, other related laboratory tests and/or result trends, tissue biopsy, etc.), the highest risk LDTs are expected to include tests that more independently drive a high-impact clinical diagnosis or treatment, with limited availability of additional information to corroborate the results. This could be incorporated into a definition under CLIA. While still being subject to development and validation requirements for analytical validity, expectations for evidence of clinical validity would be greater than for lower risk tests.

[34] 42 CFR 493.1253.
[35] Federal Register / Vol. 88, No. 190 / Tuesday, October 3, 2023, p.68017.

Additional CLIA requirements for clinical validity could be satisfied via peer-reviewed publications and clinical guidelines, local clinical trials and clinical-pathological correlations, or other acceptable means. Requirements for demonstrating clinical validity could be more thoroughly described in the inspection checklists of CLIA accreditation organizations. Laboratories would continue to be subject to PT requirements, which ensures and supports the ongoing analytical validity and quality of test results offered. The addition of regulated analytes in testing areas dominated by LDTs could further strengthen this process and provide additional transparency to the testing landscape.

8. How should Congress consider issues relating to the practice of medicine and its relationship with labeling for LDTs? Should there be additional oversight of the information conveyed to patients serviced by LDTs?

We are concerned about the impact of LDT oversight proposals and the negative impacts on the practice of medicine. We have outlined our concerns previously in the November 2023 ARUP public comment letter to the FDA, and we will re-present these concerns below. The MDA does not regulate medical activities within the laboratory, which are governed instead by the practice of medicine as permitted by state medical practice acts and in alignment with federal CLIA regulations for laboratory operations. LDT oversight proposals will conflict with some existing state medical practice acts. For example, 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,"*

and it further defines "diagnosis" as

> "(*a) to examine in any manner […] to determine the source, nature, kinds, or extent of a disease*." [36]

We are also concerned that FDA LDT oversight proposal will have First Amendment constitutional implications regarding medical speech. In this context, there should not be restriction of information conveyed to patients by clinicians, as this information is a protected form of speech and is essential for the application of medical judgment to patient care. This also underlies our primary concerns regarding the FDA's proposed rule and labeling requirements imposed upon board-certified physicians working within the laboratory.

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

As noted in our public comment letter and re-presented below, we are also concerned about the FDA's assertion that clinical laboratories are manufacturers, this time regarding the ability of laboratory scientists and physicians at academic medical centers to freely distribute scientific literature related to assays under their oversight, in accordance with restrictions under the FDA's existing "Guidance for Industry, Distributing Scientific and Medical Publications on Unapproved New Uses — Recommended Practices."[37] We believe that the proposed rule would 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.

9. Should certain CLIA regulations be updated, would it necessitate a reevaluation of the CLIA fee schedule?

If CMS were to no longer be responsible for LDT oversight (if the FDA proposed rule is enacted), then CMS should decrease its CLIA fee schedule to compensate for oversight it is no longer providing. Even with this decrease, however, we contend that clinical laboratories would not be able to afford corresponding FDA user fees, thus threatening their ability to provide affordable and essential clinical testing to patients. This is particularly important given the prior and future cuts to reimbursement created by the Protecting Access to Medicare Act (PAMA).[38]

10. What compliance challenges would legislative reforms to CLIA create? How should new regulatory requirements apply to tests currently available to patients?

The FDA proposed rule or CLIA reform would create additional compliance challenges to both clinical laboratories and accreditation organizations. Challenges include allocating limited resources to compliance functions, integrating new requirements into existing compliance programs, and the potential for duplicate, redundant, and/or conflicting requirements. LDT reform efforts under CLIA would be far less detrimental to the clinical laboratory community that then FDA's proposed rule or the VALID Act because clinical laboratories are already working with CLIA offices and CLIA accreditation organizations on a regular basis, and these agencies are also far more familiar with the clinical laboratory industry than is the FDA. Having a new FDA-oriented regulatory framework imposed upon an industry that is primarily oriented toward a pre-existing and ongoing CLIA oversight structure would be incredibly disruptive and

[37] Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices. June 2014. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/distributing-scientific-and-medical-publications-risk-information-approved-prescription-drugs-and.
[38] CLFS PAMA Educational Resources. https://www.cms.gov/medicare/payment/fee-schedules/clinical-laboratory-fee-schedule/clfs-pama-educational-resources.

detrimental to clinical laboratories, pulling resources away from helping patients and toward compliance with requirements that are ill-suited to the setting.

Lastly, we support the grandfathering of existing tests in any future regulatory oversight proposal for LDTs to ensure ongoing access to safe and essential clinical laboratory testing. Additional CLIA or FDA requirements would create an undue financial burden on laboratories, which will limit the ability of many clinical laboratories to comply with new regulations. Laboratories that cannot comply would either discontinue LDT offerings or alternatively pass additional costs on to patients. We do not believe either of these options are in the best interest of patient care and public health. We have recently made available a customer survey regarding the FDA's proposed rule, which reiterates these concerns from the broader clinical laboratory community.[39]

[39] 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.