December 4, 2023

VIA Electronic Submission to: regulations.gov

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

RE: Medical Devices; Laboratory Developed Tests [FDA-2023-N-2177]

Dear Dr. Califf:

On behalf of the Coalition for 21st Century Medicine (the "Coalition"), I am responding to your request for comments regarding the above-captioned proposed rule (the "Proposed Rule"). **The Coalition opposes finalization of the Proposed Rule as written. If the FDA insists on proceeding, however, it should significantly modify and extend implementation of the Proposed Rule to strike a more appropriate balance between the perceived need for regulatory oversight and patient access to novel, innovative tests.**

The Coalition comprises many of the world's most innovative diagnostic technology companies, clinical laboratories, physicians, venture capital companies, and patient advocacy groups working to support appropriate regulatory oversight to promote innovation in the development and use of advanced personalized diagnostic testing. Coalition members develop and perform clinical diagnostic testing, including laboratory developed tests ("LDTs"), invest in such companies, and represent patient groups whose members obtain such tests.[1] Substantial published evidence supports the analytical validity, clinical validity, clinical utility, and even economic utility of many assays offered as LDTs.

The Coalition has worked closely with FDA for nearly two decades to ensure that any new LDT regulatory framework preserves patient access to well-established LDTs, is reasonable/not overly burdensome, allows innovation to continue without unreasonable restrictions, and acknowledges the differences between laboratory procedures and kits distributed to laboratories for use in laboratory procedures. Over the years, we have engaged in mutually educational and productive

[1] The Coalition acknowledges that some groups have questioned whether FDA currently has the authority under the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 301 *et seq*.) to regulate LDTs as medical devices, including the subset of LDTs that FDA sought to define for discussion in draft FDA guidance as *In Vitro Multivariate Index Assays* (IVDMIAs). The Coalition does not address this question in this response. Consistent with the approach that the Coalition has taken throughout consideration of this issue, the Coalition's comments supportive of certain approaches to regulation should not be considered an acknowledgement by the Coalition or any of its members that FDA currently has the authority to regulate laboratory services as medical devices. In addition, these comments do not represent an admission by the Coalition or any of its members that any particular laboratory service is a "device" as that term is currently defined under Section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 321(h)).

dialogue with the leadership of the Office of Health Technology 7, and the greater Center for Devices and Radiological Health ("CDRH"). Overall, these interactions have informed efforts to identify and implement a new workable, reasonable framework for FDA oversight.

The Coalition has also worked collaboratively with Congress to provide constructive feedback on various legislative proposals, including the VALID Act.

Consistent with the Coalition's previous comments to FDA and Congress, the Coalition generally supports a new diagnostic-specific regulatory scheme with the following characteristics:

- ***FDA offers laboratories a "least burdensome" pathway to obtain marketing authorization for clinically relevant and commercially viable claims by leveraging existing laboratory validation processes.*** The framework must strike an appropriate balance between facilitating the development and delivery of innovative new tests, including those needed for rare diseases, and providing reasonable assurance of test performance. These standards should not establish unreasonable burdens to patient access. Where significant data already exists establishing the performance of on-market LDTs, FDA should rely on such data to the maximum extent possible.

- ***The regulatory requirements for each test should be risk-based and depend on the extent to which an incorrect or inaccurate result may affect patient health – not on the technology used to run the test.*** Factors for consideration include the seriousness of the condition or disease about which the test is intended to inform diagnostic or therapeutic decision-making, the materiality of the result of the test to a diagnostic or therapeutic decision, and the presence or absence of mitigating factors. Whether a test incorporates proprietary algorithms developed and appropriately validated by individual test developers is not relevant to this determination.

- ***The framework is flexible and permits reasonable modifications to tests without imposing unnecessarily burdensome regulatory requirements.*** Clinical laboratories routinely modify assays to optimize workflows, maintain access due to changes in availability of raw materials, and/or to improve assay performance. If a modification to a test is higher risk (e.g., changes the test's indication for use) or has a clinically meaningful impact on the performance of the test (e.g., materially improves sensitivity or specificity), the test developer should either submit the modification for premarket review with evidence to support the change, or validate the performance of the modified test consistent with a pre-approved protocol.[2] If a modification is lower risk (e.g., can be validated with analytical data only) or does not have a clinically meaningful impact on

[2] Congress recently granted FDA authority to permit broad use of Predetermined Change Control Plans for certain changes that would otherwise require FDA premarket submissions – including certain changes to indications for use (e.g., adding a gene to a multigene cancer screening panel). Furthermore, FDA recently published a new guidance document that introduces enforcement discretion that gives manufacturers of devices approved under a PMA or HDE to make certain changes in response to manufacturing and supply chain issues. *See* https://www.fda.gov/media/138265/download (last visited Nov. 19, 2023). We urge FDA to use this authority – and exercise/expand this creative approach to oversight of device modifications – insofar as it finalizes its plans to regulate LDTs as medical devices.

the performance of the test, the test developer should document the basis on which it reached that conclusion, and produce such documentation if requested by FDA.

- ***The framework allows for truthful, non-misleading communications between laboratories and treating physicians or between laboratories and payers to support coverage and payment for testing.*** Previous legislative proposals explicitly limited FDA's ability to regulate certain truthful, non-misleading communications in situations where such communications are unlikely to lead to patient harm (e.g., communications from clinical consultants to medical professionals as required under CLIA regulations, or communications to third-party payers). Test developers should be allowed to provide such information – including information regarding clinical utility, cost-effectiveness, and budget impact – in low-risk settings without triggering undue FDA scrutiny.

- ***The framework recognizes that LDTs are services performed in a single laboratory – not devices in any traditional sense – and therefore minimizes the overlap between FDA's quality system regulation and the Centers for Medicare & Medicaid Services's ("CMS") Clinical Laboratory Improvement Amendments ("CLIA") quality requirements.*** FDA's oversight should apply solely to so-called "manufacturing" functions undertaken by clinical laboratories (e.g., purchasing controls and reagent preparation for future use). Laboratory operations – including, without limitation, the use of FDA-cleared/listed equipment in a manner consistent with its labeling – should remain subject to regulation under CLIA and state clinical laboratory laws.

- ***The framework should be phased-in over a reasonable period.*** Enforcement discretion should end only after (a) the agency has established it has appropriate resources to timely review premarket submissions and (b) clinical laboratories have been given a reasonable opportunity to comply with a substantial new regulatory framework. The implementation timeline should be finalized only after presentation of a detailed, transparent accounting of the substantial costs that clinical laboratories will incur when coming into compliance with the new requirements, and consideration of whether such laboratories can comply with such requirements on such timeline given existing limitations on laboratory resources and availability of investment capital.

* * * *

The Coalition continues to believe that a diagnostics-wide, comprehensive approach to oversight of all testing (including LDTs) – such as those that have been considered in Congress – would be preferable to treating all diagnostics as medical devices under the Food, Drug, and Cosmetic Act (FDCA). As such, we oppose finalization of the Proposed Rule as written, which would apply the FDCA's medical device framework to laboratory procedures.

If the FDA insists on proceeding under the FDCA, however, it should significantly modify and extend implementation of the Proposed Rule to strike a more appropriate balance between the perceived need for regulatory oversight and patient access to novel, innovative tests. Our recommended revisions are as follows:

1. **FDA should require clinical laboratories performing LDTs to register their facilities, list their LDTs, and submit adverse event information before proposing a concrete timeline for compliance with other regulatory requirements (e.g., quality systems and premarket review requirements).**

The Proposed Rule would end longstanding LDT enforcement discretion in five stages over a four-year period from the date FDA publishes a final rule:

- *Phase 1 (effective one year post-finalization)*: Clinical laboratories must comply with prospective medical device (adverse event) reporting and correction/removal reporting requirements.
- *Phase 2 (effective two years post-finalization)*: Clinical laboratories must comply with all other device requirements (*e.g.*, registration/listing, labeling, investigational use), except for quality systems and premarket review.
- *Phase 3 (effective three years post-finalization)*: Clinical laboratories must comply with quality systems requirements.
- *Phase 4 (effective three and a half years post-finalization, but not before October 1, 2027)*: Clinical laboratories must comply with premarket review requirements for high-risk tests (*i.e.*, tests subject to premarket approval ("PMA") requirement).
- *Phase 5 (effective four years post-finalization, but not before April 1, 2028)*: Clinical laboratories must comply with premarket review requirements for moderate- and low-risk tests (*i.e.*, tests subject to *de novo* or 510(k) requirement).

Unfortunately, FDA proposes this timeline without the benefit of certain critical information necessary to evaluate the feasibility of FDA's plans. This information should include clear and transparent answers to the following questions:

- How many clinical laboratories currently offer LDTs?
- How many LDTs are currently on the market?
- How frequently are LDTs modified, and what is the nature of those modifications?
- What are the intended use(s) of those LDTs?

The Proposed Rule allows FDA to collect this information starting one or two years post-finalization (Phase 1/Phase 2). However, it is premature for FDA to establish definitive timelines for compliance with Phase 3 (quality systems) and 4/5 (premarket review) requirements until it has obtained this critical information. **Without answers to these key questions, it is not possible to evaluate the feasibility of FDA's proposed timeline, or to assess whether FDA's proposal appropriately focuses the Agency's limited resources on problematic tests.**

Notwithstanding any research that FDA may have completed to inform its plans, no publicly available resource provides a definitive answer to these critical questions. Indeed, the Proposed Rule does not contain any explicit estimate of the Agency's expected workload. We note, however, that the following objective statistics *suggest* the proposed regulatory timeline may impose a significant – and potentially unmanageable – administrative burden on the FDA:

- *CLIA allows at least 33,000 clinical laboratories nationwide to perform LDTs.* Under CLIA rules, a clinical laboratory may only perform an LDT if authorized to perform "high" complexity testing.[3] CLIA requires clinical laboratories to obtain a Certificate of Compliance or Certificate of Accreditation to perform "high" complexity testing.[4] 33,008 clinical laboratories (16,964 operating under a Certificate of Compliance, 16,044 operating under a Certificate of Accreditation) currently operate under one of these two Certificate types.[5]

- *New York State has approved (or conditionally approved) thousands of tests offered as LDTs.* A clinical laboratory cannot offer most LDTs to New York residents until it successfully obtains test-specific approval from the New York State Department of Health ("Wadsworth"). As of November 2, 2024, Wadsworth has approved 10,204 applications (or supplements thereto) for LDTs.[6]

Unfortunately, our concerns about the FDA's ability to manage thousands of (potential) applications are not without factual basis. The Coalition appreciates the FDA's extraordinary efforts to ensure the quality and performance of COVID-19 tests, and understands the pandemic placed an unexpected burden on Agency staff, forcing the diversion of resources in real-time from other important projects. However, the FDA itself has acknowledged that the burden of managing the volume of pre-EUA and EUA submissions for this single group of tests caused the Agency to miss user fee deadlines for other types of tests, and to outright decline pre-submission meeting requests for virtually all other tests for more than a year:

> *Unquestionably, our biggest review challenges have been in the IVD product space due to the enormous volume of EUA submissions. In the last year, we've already taken extraordinary steps to prioritize the review of COVID-19-related IVD submissions.* ***Unless IVD pre-submissions are related to COVID-19, companion diagnostics, a breakthrough designation request, or have a significant public health impact, we have been unable to review them.*** *We have tried to utilize all the tools at our disposal.* ***However, for the remainder [of 2021], we will be declining other IVD pre-submission requests that don't fall into these categories for the present time. In addition, non-COVID-19 IVD submissions are experiencing longer-than-typical review timelines and delays in initiation of review.***[7]

---

[3] Centers for Medicare & Medicaid Services, CLIA Overview, CLIA Overview… (cms.gov) (last visited Nov. 2, 2023).
[4] 42 C.F.R. §§ 493.49, 493.55.
[5] Division of Clinical Laboratory Improvement and Quality (September 2023), CLIA Stats (cms.gov). Note, the ~33,000 figure may be substantially higher, as it does not include any of the ~15,000 clinical laboratories licensed solely in the CLIA-exempt states of New York and Washington.
[6] Department of Health (Wadsworth Center), Search Approved Laboratory Developed Tests, Search Approved Laboratory Developed Tests | New York State Department of Health, Wadsworth Center (last visited Oct. 31, 2023).
[7] U.S. Food and Drug Administration, A Year Into the Pandemic: How the FDA's Center for Devices and Radiological Health is Prioritizing its Workload and Looking Ahead (Apr. 15, 2021), A Year Into the Pandemic: How the FDA's Center for Devices and Radiological Health is Prioritizing its Workload and Looking Ahead | FDA (emphasis added).

The Coalition understands the Agency intends to address these issues by hiring additional staff with funds from the next user fee bill, and by leveraging third-party reviewers (where appropriate). In general, the Coalition supports the concept of expanding FDA's review capabilities by delegating review responsibility to third parties with experience reviewing analytical and clinical validity data. However, even if the Agency successfully adds staff and secures access to qualified third-party reviewers, it is unclear how the Agency can assure test developers, clinicians, and patients that it will have sufficient resources to timely respond to laboratory pre-submissions and marketing submissions without answers to these fundamental questions. Otherwise, how will FDA know how many reviewers, including third party contractors. To hire (and with what expertise)? Or how many third-party reviewers to engage (and with what expertise)? Direct experience to date with FDA contracted third-party reviewers assigned to COVID-19 LDTs suggests that reliance on such contractors for review of more complex LDTs will, at best, yield longer review timelines and inconsistent outcomes. We understand that FDA has engaged a consulting company to perform LDT reviews on a contract basis; however, the sole source nature of that contract and the lack of transparency by the FDA regarding how this consulting firm plans to address actual and/or perceived conflicts of interest further suggests that the Proposed Rule's timeline for pre-market submissions is inadequate to ensure a smooth transition with consistent outcomes among LDTs.

Moreover, FDA's reliance on the third-party review program for most LDTs does not acknowledge the longstanding problems with the third-party review program.[8] For example, FDA's practice of re-reviewing third-party evaluations risks inconsistent communications with LDT developers when FDA raises new review issues that were not raised by the third-party reviewer. This practice not only results in significant added burden (direct costs and delays) for applicants who rely on the communications from the lead reviewer, but also squanders valuable FDA resources and reviewer time for re-reviews.

Additionally, FDA does not appear to have considered the practical and operational challenges if it relies on existing laboratory regulators to enforce FDA regulatory requirements. While the entities who currently oversee clinical laboratories and LDTs have substantial experience applying CLIA and/or accreditation organization standards, such organizations may struggle to apply FDA's "medical device" rules to clinical laboratory activities, particularly insofar as application of FDA's rules would be inconsistent with or contradictory to longstanding laboratory procedures (e.g., clinical consultation requirements) . Insofar as such reviewers represent a critical component of FDA's plans to manage application workload, FDA should not proceed to require pre-market submissions for LDTs until the Agency demonstrates in a pilot program that such third-party reviewers can also apply FDA's overlapping and potentially inconsistent rules in a manner that is truly "least burdensome" for clinical laboratories running LDTs. Additionally, FDA should not plan to make reliance on third-party review a substantial portion of its plans to manage the anticipated volume of LDT submissions until the Agency

[8] Miller BJ, Blanks W, Yagi B. The 510(k) third party review program: promise and potential. *J Med Syst* 2023;47(1):93: doi: 10.1007/s10916-023-01986-5. ("Despite the best of intentions, the third party review program has struggled. Utilization declined from a peak of 9.3% in 2008 to 2.4% in 2020, a decline due to a multitude of factors. First, potentially low quality reviews by third party review organizations routinely lead to FDA re-reviews, an issue that became increasingly common during the pandemic (2021–2022). FDA decision-making on third-party reviews slowed while re-reviews increased, with the share of applications "pending final decision" increasing from 0% in FY2018-2020 to 8% in 2021 to 30% in 2022.")

eliminates routine re-review of Third-Party reviews. Furthermore , FDA should formally withdraw inconsistent and outdated guidance, in particular the IVDMIA draft Guidance(s), as they are inconsistent at best with current approaches and will serve only to confuse both LDT developers new to FDA regulatory and quality requirements, as well as the vast number of additional reviewers needed to achieve FDA's proposed new regulatory scheme.

The agency's lack of clarity on these critical points creates the risk of meaningful delays in FDA review processes, potentially threatening patient access to critical, standard-of-care LDTs.

To reduce the chances of an avoidable administrative backlog, the Coalition strongly encourages FDA to rescind the quality systems and premarket submission components of the Proposed Rule until it has actual data to inform critical assumptions regarding its expected workload. Then, after FDA has collected and reviewed this information, FDA should propose an updated timeline for compliance with these requirements.

The Coalition understands the Agency believes it can mitigate administrative risks by allowing LDTs to remain on the market while premarket review submissions are under review by Agency (or third-party review) staff. However, the Agency provides no explicit guidance on how it intends to respond when it reviews an application that is not immediately approvable. For example:

- Will FDA allow LDTs to remain on the market while test developers address FDA's questions? If so, for how long? And how much time will FDA give test developers to respond to questions?
- Must laboratories resubmit (and pay additional user fees) if FDA requires additional studies that cannot be performed within the agency's mandated response time?
- What standard will FDA use to decide whether a test can remain on the market while the laboratory addresses these questions?
- If a laboratory disagrees with FDA's decision, will it have any formal appeal rights?

The Proposed Rule's failure to establish clear guardrails for (a) how it will respond to applications that are not immediately approvable and (b) the Agency's process after receiving and reviewing an application that is not technically approvable but raises minor issues leaves patients, providers, and clinical laboratories without assurance of continued access to standard of care LDTs. **The Coalition urges FDA to clarify that LDTs can remain on the market while addressing FDA's questions unless the assay is likely to cause or contribute to a deaths or serious injuries if it remains on the market.**

2. **<u>When the FDA implements its quality systems and premarket review requirements, it should exercise continued enforcement discretion for "high quality" tests</u>.**

Throughout FDA's consideration of LDT oversight, FDA has acknowledged that it should phase in its regulatory requirements to initially focus on those tests that may be most likely to cause patient harm. In the 2014 Draft Guidance, for example, the framework would have required compliance with FDA regulatory requirements up to nine years post-finalization for lower-risk

LDTs.[9] In fact, in its 2017 White Paper, FDA proposed a different approach, under which it would have continued enforcement discretion for LDTs currently on the market, unless FDA "clawed back" such tests due to performance concerns.[10] Unfortunately, the Proposed Rule reflects a far more aggressive timeline than any recently proposed by FDA, and therefore threatens patient access to critical, standard of care LDTs.

According to the Proposed Rule, the Agency's motivation to suddenly impose "device" regulatory requirements in a short time frame is driven largely by its experience with LDTs offered during the COVID-19 PHE, as well as a handful of other news stories. We do not, however, believe it is reasonable or appropriate to question the validation and development practices of an entire class of providers based solely on this limited subset of information. This is particularly true insofar as some LDT providers have a longstanding, verifiable track record of performing high-quality tests. Indeed, the Agency appears to acknowledge this concern, as the Proposed Regulatory Impact Analysis ("PRIA") includes similar approaches in Alternatives 3 and 5.

To ensure FDA initially targets its limited resources towards poor-performing tests, we recommend that FDA indefinitely extend enforcement discretion (i.e., "grandfather") from quality systems and premarket review requirements for "high quality" tests on the market prior to the effective date of the Final Rule. For "high quality" tests first introduced after the effective date of the Final Rule (or pre-Final Rule tests substantially modified[11] after the effective date of the Final Rule), we recommend that FDA extend enforcement discretion for an additional five years beyond its scheduled implementation of such requirements for LDTs more generally. Under our proposal, LDTs would be considered "high-quality" if they meet any one of the following criteria:

- Receive test-specific approval from Wadsworth;
- Receive coverage from the Palmetto GBA Molecular Diagnostic ("MolDX") Program following successful submission of a test-specific Technical Assessment ("TA"); OR
- Are performed in a CLIA-certified clinical laboratory that has received accreditation from the College of American Pathologists ("CAP");

Furthermore, consistent with the approach taken (with FDA's input) in the VALID Act, the Agency should only end such "enforcement discretion" for a test in one of the above-described groups insofar as credible information establishes that (a) an LDT is marketed with insufficient evidence of analytical validity or clinical validity; (b) an LDT is marketed with any false or misleading analytical or clinical claims; or (c) it is probable an LDT will cause serious adverse health consequences.

As requested, please find an overview of the "specific characteristics… and activities within these programs [that] justify such an approach" – with a particular focus on the aspects of each

[9] U.S. Food and Drug Administration, Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) (October 2014), Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) | FDA.
[10] U.S. Food and Drug Administration, Discussion Paper on Laboratory Developed Tests (LDTs) (Jan. 13, 2017), https://www.fda.gov/media/102367/download.
[11] For purposes of this framework, a test would be "substantially modified" if it materially changes the test's indication for use or has a clinically meaningful impact on the performance of the test.

program that provide FDA with reasonable assurance that the LDTs described therein provide analytically and clinically valid test results to patients and health care providers.

a. *Test-specific approval for LDT from Wadsworth*

New York State law prohibits clinical laboratories from offering many LDTs to NYS residents without first obtaining test-specific approval from Wadsworth. Wadsworth classifies LDTs into one of five categories – high risk, moderate risk, low risk, clinical trial, and lifestyle – based on the level of risk associated with the test. Clinical laboratories only receive full approval for high and moderate risk tests only *after* a detailed review of the underlying evidence:[12]

Category	Submission required?	Initial Approval	Review required	Review Priority
High	Yes	None	Yes	High[1]
Moderate	Yes	Conditional[2,3]	Yes	Medium
Low	Yes	Full[2,3]	No[4]	--
Clinical Trial	Yes	N/A[2,4]	No[4]	--
Lifestyle	Yes	N/A[2,4]	N/A[4]	--

[1]Submissions for laboratories pending a permit or permit category are automatically assigned High Risk unless the package meets the conditions for Clinical Trial or Lifestyle.

[2]Provided the laboratory holds the appropriate permit category.

[3]The department reserves the right to withhold approval at its discretion.

[4]The department reserves the right to review all applications at its discretion.

An LDT application must include the following documentation for review by Wadsworth:

- General information (lab information, test name/methodology/analytes);
- Summary of validation study (e.g., establishment/verification of performance specifications);
- Marketing/educational materials;
- Standard operating procedures;
- Copies of literature references supporting the clinical validity of the test;
- Narrative summary of analytical validation studies (e.g., specimen stability, specimen storage conditions/time, accuracy, precision, reportable range, analytical sensitivity, analytical specificity);
- Narrative summary of clinical validation studies (e.g., protocols, process for blinding status during testing, procedure for resolving discrepant results, clinical sensitivity and specificity, data reduction and interpretation (including algorithmic processes)
- Data from representative specimen run;
- Quality control data;
- Sample test requisition form; and

[12] New York State Dep't of Health, Tiered Evaluation of Laboratory Developed Tests Policy, NYSDOH Policy for risk-based Evaluation of ldts (wadsworth.org) (last visited Nov. 2, 2023).

- Sample reports for all applicable findings, including interpretive text, assay limitations, and required disclaimers.[13]

Wadsworth also imposes additional, test-specific requirements for certain types of LDTs (e.g., cellular immunology, cytogenetics, genetic testing, microbiology (molecular), oncology (molecular), toxicology) based on the unique characteristics of those assays.[14]

After reviewing this information, Wadsworth decides whether the test will receive approval for offering to NYS residents.

Based on the strength of its review process, FDA accredited Wadsworth as a third-party reviewer for IVDs for molecular diagnostic tests for patients with cancer.[15]

Furthermore, from a quality systems perspective, Wadsworth inspects clinical laboratories performing LDTs for compliance with its Standards of Practice. Wadsworth "general" standards include requirements for quality management systems addressing:

- Equipment and supply verification;
- Reagent qualification and verification;
- Specimen processing
- Test procedures (including quality; controls);
- Test result review and reporting;
- Document and specimen retention;
- Proficiency testing; and
- Investigations and corrective actions.[16]

The state imposes additional quality requirements based on the specialty(ies) in which the clinical laboratory performs testing, such as cytogenetics, genetic testing, microbiology, and oncology.[17]

b. *Successful TA for LDT from MolDX*

The MolDX Program creates coverage policies for molecular (DNA and/or RNA) tests for use by Medicare administrative contractors. Under MolDX rules, a molecular LDT is only eligible for Medicare coverage if MolDX reviews and approves a TA confirming the analytical validity, clinical validity, as well as the clinical utility of the assay:

---

[13] New York State Dep't of Health, General Assay Approval, STATE OF NEW YORK (wadsworth.org) (last visited Nov. 2, 2023).
[14] New York State Dep't of Health, Test Approval, Test Approval | New York State Department of Health, Wadsworth Center (last visited Nov. 2, 2023) (materials posted under "Making a Submission" tab).
[15] U.S. Food and Drug Administration, FDA Unveils a Streamlined Path for the Authorization of Tumor Profiling Tests Alongside Its Latest Product Action (Nov. 15, 2017), FDA unveils a streamlined path for the authorization of tumor profiling tests alongside its latest product action | FDA.
[16] New York State Dep't of Health, Clinical Laboratory Standards of Practice: General Systems Standards (May 5, 2021), EFFECTIVE_GeneralSystems_May2021_FINAL.pdf (wadsworth.org).
[17] New York State Dep't of Health, Laboratory Standards, Laboratory Standards | New York State Department of Health, Wadsworth Center (last visited Nov. 2, 2023).

> *Molecular Diagnostic Services Program (MolDX®) will review all new test/assay clinical information to determine if a test meets Medicare's reasonable and necessary requirement. Labs must submit a comprehensive dossier on each new test/assay prior to claim submission. MolDX® will only cover and reimburse tests that demonstrate analytical and clinical validity, and clinical utility at a level that meets the Medicare reasonable and necessary requirement.*[18]

Clinical laboratories must submit the following documentation as part of a MolDX TA:

- Complete analytical and clinical validation documents;
- Sample reports;
- Copy of test requisition form;
- Documentation of final test approval by Wadsworth (if any), as well as any written questions (and the laboratory's response to the same);
- Documents that summarize key aspects of the test's analytical and clinical validation; and[19]
- Peer-reviewed publications establishing the assay's clinical validity (where required by the assay's local coverage determination).[20]

The specific requirements of the summary documents are targeted based on individual assay characteristics,[21] and generally require clinical laboratories to submit detailed information establishing the analytical and clinical validity of the assay, including specimen-level data. For example, the general "Technical Assessment (TA) Summary Worksheet" summary document requires clinical laboratories to provide:

- Detailed overview of the test (e.g., general test information, methodology, analytical sensitivity, analytical specificity, precision, reference intervals, quality control/quality management);
- Summary of assay performance in contrived specimens and clinical specimens (e.g., concordant positives, concordant negatives, sensitivity, specificity, and linear regression results for method comparison (with 95% confidence intervals), separated out by analyte);
- Specimen-level data for contrived and clinical specimens (e.g., sample identifier, sample type, source, expected results, expected results methodology, observed results, and discordance resolution); and

---

[18] MolDX: Molecular Diagnostic Tests (MDT) (L35025), LCD - MolDX: Molecular Diagnostic Tests (MDT) (L35025) (cms.gov) (last visited Nov. 2, 2023).
[19] Palmetto GBA, Technical Assessment Submission Checklist and Questionnaire (GEN-CQM-003-v1), https://www.palmettogba.com/palmetto/providers.nsf/files/Technical_Assessment_Checklist_(GEN-CQM-003).pdf/$FILE/Technical_Assessment_Checklist_(GEN-CQM-003).pdf (last visited Nov. 2, 2023).
[20] *See, e.g.,* MolDX: Minimal Residual Disease Testing for Cancer (L38779) (last visited Nov. 2, 2023), LCD - MolDX: Minimal Residual Disease Testing for Cancer (L38779) (cms.gov) ("This Contractor provides limited coverage for MRD testing in cancer when ALL of the following are true: (…) Clinical validity (CV) of any analytes (or expression profiles) measured must be established through a study published in the peer-reviewed literature for the intended use of the test in the intended population.")
[21] Palmetto GBA, Technical Assessment Forms, https://www.palmettogba.com/palmetto/moldxv2.nsf/DID/TJ4XC2M5IX (last visited Nov. 2, 2023).

- Summary of published literature establishing clinical validity and clinical utility (e.g., elements of study design, sample size, primary and secondary endpoints, and associated statistical analyses.[22]

MolDX requests similar information in specialized summary forms for certain assays (e.g., next generation sequencing for solid tumors or inherited cancer, minimal residual disease, molecular risk stratification, syndromic infectious disease panels, and allograft rejection tests).[23]

The MolDX medical directors – three of whom are board-certified pathologists, and one of whom is a molecular geneticist[24] – and their supporting staff review all data included in the Technical Assessment documents before deciding to approve an LDT for Medicare payment.

c. *Performance in CAP-accredited, CLIA-certified clinical laboratory*

Clinical laboratories may obtain authorization to perform high complexity tests – including LDTs – by seeking accreditation from CAP. CAP-accredited clinical laboratories must comply with applicable standards to maintain accreditation.[25] CAP accreditation standards impose several general and specialty-specific requirements on clinical laboratories, including requirements related to the analytical and clinical validation of testing services offered as LDTs. For example, the CAP "Molecular Pathology" checklist requires laboratories to take the following analytical validation steps before clinical use of a novel assay:

> *Prior to clinical use of each modified FDA-cleared/approved test and laboratory-developed test (LDT), the laboratory has performed a validation study and prepared a written assessment of each of the following test method performance specifications, as applicable, using a sufficient number of characterized samples:*
>
> - *Analytical accuracy*
> - *Analytical precision/reproducibility*
> - *Reportable range*
> - *Analytical sensitivity (lower detection limit)*
> - *Analytical specificity*
> - *Any other performance characteristic required to ensure analytical test performance (eg, specimen stability, reagent stability, linearity, carryover, and cross-contamination.*[26]

Similarly, with respect to clinical validity, CAP requires:

---

[22] Palmetto GBA, Technical Assessment (TA) Summary Worksheet (GEN-PF-001-v4), https://www.palmettogba.com/palmetto/providers.nsf/Files/Technical_Assessment_Summary_Form_GEN-PF-001.xlsx/$FILE/Technical_Assessment_Summary_Form_GEN-PF-001.xlsx (last visited Nov. 2, 2023).
[23] Palmetto GBA, Technical Assessment Forms, https://www.palmettogba.com/palmetto/moldxv2.nsf/DID/TJ4XC2M5IX (last visited Nov. 2, 2023).
[24] Palmetto GBA, Frequently Asked Questions (Oct. 20, 2023), MolDX - Frequently Asked Questions (palmettogba.com) (identifying the medical directors under question 9 "Who the Medicare Administrative Contractor (MAC) Medical Directors of Palmetto GBA?").
[25] 42 C.F.R. § 493.61(b)(3).
[26] College of American Pathologists, Molecular Pathology Checklist (Aug. 24, 2023), at MOL.31130.

> *The clinical performance characteristics of each assay are determined and recorded, using either literature citations or a summary of internal study results.*
>
> *(…)*
>
> *Clinical performance characteristics should be determined relative to a combination of clinical data (eg, biopsy findings, radiographic and clinical findings, other laboratory results, etc.). Establishing clinical validity may require extended studies and monitoring that go beyond the purview or control of the individual laboratory.* ***The laboratory should perform clinical validation in-house, except in the case of very rare conditions, in which case data from the literature can be used, or in the case of very common conditions for which the clinical validity is well-established in the literature.*** *It is essential that the laboratory director or designee use professional judgment in evaluating the results of such studies and in monitoring the state-of-the-art worldwide as it applies to newly discovered gene targets and potential new tests, especially those of a predictive or incompletely penetrant nature.*[27]

CAP-accredited clinical laboratories are subject to inspection for compliance with these and other quality requirements on a biannual basis.[28] These other requirements include the following:

- Qualification and maintenance of reagents, instruments, and equipment;
- Review and evaluation of complaints;
- Corrective actions;
- Development and maintenance of procedure manuals;
- Personnel;
- Physical facilities;
- Proficiency testing;
- Specimen collection and handling; and
- Results reporting.[29]

Clinical laboratories that fail to comply with these requirements are subject to enforcement action, such as certificate suspension, limitation, revocation, or directed plans of correction.[30]

Insofar as other CLIA-recognized accreditation organizations provide similar oversight with respect to LDT performance – particularly as it relates to assurance of analytical and clinical validity – the Coalition believes such assays should also be eligible for indefinite or extended enforcement discretion, as applicable.

* * * *

[27] *Id.* at MOL.31590.
[28] College of American Pathologists, Inspection Tools and Training, Inspection Tools and Training | College of American Pathologists (cap.org) (last visited Nov. 2, 2023).
[29] College of American Pathologists, "General" and "Common" Checklists (2023).
[30] 42 C.F.R. § 493.1806(b), (c).

The Coalition recommends that FDA recognize all three of these standards for indefinite or extended enforcement discretion because individual laboratories performing LDTs may not participate (or be eligible to participate) in all three programs. For example, an academic medical center located in the Pacific Northwest that only tests specimens from local patients would have no reason to seek test-specific approval from Wadsworth, which is only required for testing performed on specimens from New York State residents. Similarly, a clinical laboratory located outside of the MolDX Program's jurisdiction[31] would not have the option of submitting a detailed TA.

The Coalition believes that all LDTs meeting one of these three standards – regardless of whether performed in independent laboratories, academic medical center laboratories – should be eligible for continued enforcement discretion. The Coalition does not, however, support continued enforcement discretion based on where or by whom the test is developed; enforcement should be risk-based, not entity-based. For example, the Coalition does not support continued enforcement discretion for tests solely because those tests are performed in an academic medical center (AMC) laboratory. We are not aware of any risk-based characteristics that are unique to AMCs and different from other commercial laboratories, and it is unclear to us how the Agency's concerns about assay performance are mitigated by performance in the AMC setting. Furthermore, as FDA is aware, many AMC laboratories effectively operate as national or regional reference laboratories.

3. **The FDA should more carefully consider the costs incurred by clinical laboratories in complying with these additional regulatory requirements.**

The PRIA contains a summary of the Agency's assumptions regarding the costs that clinical laboratories running LDTs will incur when coming into compliance with FDA's requirements for medical devices. While C21 appreciates the FDA's efforts to explain its reasoning, we are concerned that these assumptions do not fairly reflect the incremental costs to clinical laboratories. For example:

- *The PRIA's primary cost estimate for compliance with FDA's quality systems regulation appears to substantially underestimate the cost of laboratory compliance.* On pages 72-73 of the PRIA, FDA estimates $72.56 million in one-time costs for ~1,200 clinical laboratories to implement an FDA-grade quality system. Therefore, *on average*, FDA appears to assume that a clinical laboratory can implement an FDA-compliant quality system for ~$60,000. Unfortunately, this figure likely substantially underestimates the actual cost of compliance.[32] Indeed, this figure does not cover even half of the estimated annual salary for a single employee with FDA QSR skills/experience,[33] let alone the substantial additional costs that many laboratories may incur with respect to information technology enhancements and outside consultant fees.

---

[31] Palmetto GBA, Molecular Diagnostic Program (MolDX) Coverage, Coding, and Pricing Standards and Requirements (M00106), MolDX Manual (palmettogba.com), at § 1.2 (last visited Nov. 2, 2023).
[32] Fuhr T. Makarova E, Silverman S, Teplis V. Capturing the value of good quality in medical devices (Feb. 24, 2017), https://www.mckinsey.com/industries/life-sciences/our-insights/capturing-the-value-of-good-quality-in-medical-devices ("We estimate the total direct cost of quality at 6.8 to 9.4 percent of industry sales.").
[33] *See* https://www.salary.com/research/salary/skill/fda-quality-systems-regulations-qsr-salary (last visited Nov. 20, 2023) (quoting an average base salary of $134,490 for "jobs with FDA [QSR] skills").

- *Lack of existing regulatory teams with experience applying FDA quality systems requirements to clinical laboratories – and increased demand for those same individuals – will further exacerbate costs.* While CLIA-certified clinical laboratories must currently comply with CLIA, accreditation organization, and/or state quality systems requirements, the teams responsible for such compliance do not generally have experience complying with FDA's quality systems requirements (and/or ISO 13485, if FDA harmonizes Part 820 as expected). To date, FDA has approved/cleared just a small number of single-site IVDs – so a relatively small population of individuals have direct experience applying FDA's QS requirements in a clinical laboratory setting. If finalized, the Proposed Rule would create demand for regulatory specialists that far exceeds the existing supply of regulatory specialists. Furthermore, FDA's own increased demand for such specialists may further exacerbate the impact of this anticipated shortage.

4. <u>The FDA should clarify several key aspects of the Proposed Rule</u>.

The Proposed Rule leaves several key questions unaddressed and unanswered. Without information on the following points, it is impossible to know how burdensome this proposal will be on clinical laboratories, **As such, the Coalition respectfully requests that FDA address all these points in any potential final rule.**

- How many premarket review submissions (PMA, *de* novo, or 510(k) does FDA expect to receive?

- In detail – where will FDA find the resources necessary to regulate LDTs (e.g., to participate in pre-submission meetings, inspect laboratories, and review premarket submissions)? How does FDA plan to accommodate its increased workload (e.g., pre-submissions) *prior* to MDUFA VI (particularly insofar as under the current timeline, FDA is unlikely to have much information about the number/types of LDTs in 2026 when the Agency would typically begin MDUFA negotiations? And how will competing with industry for regulatory professionals impact FDA's plans to ramp up its own capacity?

- How will laboratories know whether their tests are high, moderate, or low risk? Will FDA develop and make available to clinical laboratories *at the time the rule is finalized* an LDT-specific "policy navigator" like that which the Agency developed for digital health applications,[34] which includes up to date information and links to all relevant guidance to assist laboratories in making initial risk classifications and coming into compliance with other FDA regulatory requirements? And what are the consequences if the lab makes the wrong decision?

    - The Coalition understands that FDA has guidance available regarding the regulatory classification for certain assays. For novel/proprietary assays, however, such guidance is unlikely to be available – particularly with respect to

[34] *See* https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-policy-navigator (last visited Nov. 19, 2023)

whether such assays are subject to the PMA or *de novo* pathways. As such, the Coalition strongly recommends that FDA clarify it will not take enforcement action against clinical laboratories who make a good faith effort to evaluate whether their tests are high, moderate, or low risk, and have otherwise complied with the Agency's registration, listing, and adverse event reporting requirements.

- How will FDA decide which submission (within a class of submissions) will be reviewed as a *de novo*, and which will be reviewed as a 510(k)? What if FDA receives multiple submissions for the same (novel) intended use on the same day?

- To what extent will FDA consider unmet patient needs – e.g., due to diagnosis with a relatively rare condition, or lack of access to health care more generally – when deciding how to prioritize the development of guidance or other materials intended to help laboratories come into compliance, or reviewing applications for marketing authorization?

- When labs make a premarket submission, what will happen to tests for which FDA requests additional information? Can those tests remain on the market while the lab responds to FDA's concerns, or must the lab pull the test from the market? On what basis will FDA make this determination, and will there be an opportunity for the laboratory to appeal?

- CLIA already regulates laboratory operations – including for labs that run FDA-reviewed test kits. Minimizing overlapping, inconsistent and potentially duplicative regulation between FDA and CLIA will strengthen laboratory oversight while seeking to ensure the new framework would impose the *least burdensome* approach to regulating important diagnostic services. Each jurisdictional body should have specific, defined authority, which should reduce the risk of conflict and ambiguity. How will FDA ensure the imposition of its requirements do not conflict with CLIA requirements (e.g., with respect to the clinical consultation requirements under 42 C.F.R. § 493.1419)? And how will FDA ensure parity between its oversight of kit-based tests where the Agency does not regulate how those tests are run once approved and LDTs?

    - Establishing an FDA-compliant quality system is incredibly labor- and cost-intensive – even for those high-quality clinical laboratories who can leverage certain existing policies and procedures initially developed to comply with CLIA, CAP, and/or state clinical laboratory requirements. We understand this process can take multiple years, and can cost hundreds of thousands of dollars to come into compliance (see above), in addition to the substantial costs that clinical laboratories already incur to establish quality systems to meet CLIA and state clinical laboratory requirements.

- Historically, the FDA has acknowledged that clinical laboratories that would be newly subject to FDA regulation may need substantial assistance in determining how their existing quality systems can be leveraged to meet FDA's QSR. Will FDA make any guidance available to clinical laboratories (e.g., regarding quality systems)? And if so, on

what timeline/will that availability give laboratories enough time to comply with FDA standards?

- FDA has indicated that it intends to harmonize its quality systems regulations (QSR) with ISO 13485 by the end of this year (December 31, 2023). To comply with the quality systems provisions of the Proposed Rule, clinical laboratories must first perform a quality gap assessment – preferably as soon as possible – to meet the Proposed Rule's timeline, particularly since validation data intended to support premarket submissions must be developed under an FDA compliant quality system. In the absence of clarity regarding these requirements, clinical laboratories will need to prepare to comply with ISO13485 and QSR – a time and labor-intensive process requiring new FTEs and new systems that may need to be repeated, at least in part, when FDA finishes harmonization. Requiring such duplicative work is not consistent with the Agency's "least burdensome" principles.

- To what extent will FDA make materials available specifically intended to help small businesses come into compliance? Will FDA take efforts to proactively inform industry about the benefits of being an FDA-designated "small business," including substantially reduced user fees[35] (if continued in MDUFA VI)?

* * * *

In conclusion, the Coalition opposes finalization of the Proposed Rule as written, and encourages FDA to continue working with stakeholders to develop an updated legislative framework that applies to all diagnostic testing, including LDTs. If the FDA insists on proceeding under the FDCA, however, it should significantly modify and extend implementation of the Proposed Rule to strike a more appropriate balance between the perceived need for regulatory oversight and patient access to novel, innovative tests.

The Coalition appreciates the opportunity to provide comments on the Proposed Rule, and would welcome the opportunity to continue working with FDA to craft solutions to the issues raised herein.

If you have any questions about these comments, please contact me via electronic mail to hmurphy@c21cm.org.

Sincerely yours,

Hannah Murphy

[35] U.S. Food and Drug Administration, Reduced Medical Device User Fees: Small Business Determination (SBD) Program (Oct. 31, 2022), https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/reduced-medical-device-user-fees-small-business-determination-sbd-program.

Executive Director
The Coalition for 21st Century Medicine