Subject: Take Action: FDA Proposed Rule on LDT Regulation

Dear APC Members:

The Association of Pathology Chairs shares the serious concerns of many of our members and other professional organizations regarding the FDA's recently proposed rule (Docket #FDA-2023-N-2177) for regulation of laboratory developed tests (LDTs) as medical devices within existing regulatory frameworks.

The APC will be submitting a formal response to the FDA regarding what we believe would be the consequences of implementation of this rule and we are working to align with other organizations and professional groups in order to have a strong, uniform response that represents the interests of our laboratories and the patients we serve.

We encourage our member departments to provide comments on the rule, ideally in cooperation with the government relations offices of your medical schools, hospitals, and hospital systems, to provide institutional responses that reflect the grave concerns that academic medical centers, and all of the clinical specialties they represent, harbor regarding the proposed rule. The deadline for response is December 4, 2023. Instructions for submitting comments are detailed at the top of the proposed rule; go to https://www.regulations.gov *and enter the docket number above.*

In your response, we encourage you to include the following key points to amplify the concerns of the APC and other members of the academic laboratory community:

- Request an extension to the FDA's deadline for response to at least 120 days, since this is an important issue that deserves appropriate research and consideration, and especially since the FDA has requested data for evidence-based decision-making. APC is advocating with other organizations for an extension to the comment period.
- LDTs do not only encompass esoteric tests for rare diseases, but also include numerous laboratory tests that are routinely employed to care for the complex patients seen in academic medical centers. Examples include (but are not limited to) therapeutic drug monitoring for transplant and infectious disease patients; leukemia/lymphoma characterization by flow cytometry; tissue characterization by immunohistochemistry; molecular detection of cancer mutations that inform specific therapies in real time; cytogenetic analysis of genes and chromosomes; and microbiological tests for common, uncommon, and emerging disease.
- Include department-specific data for illustration, such as the number of tests your lab(s) perform that would be considered LDTs under FDA regulation, how many of those tests were used over the last 10 years to diagnose and treat patients, and how many would no longer be offered (presumptively) because of insurmountable and duplicative burdens of the proposed FDA regulatory process and the predicted impact to patients and community. Data demonstrating the quality and safety of your LDTs and frequency at which these are replaced by FDA-approved tests would also be important and meaningful. The FDA has specifically asked for data in order to provide an evidence-based rule.
- The FDA should be lauded for its commitment to patient safety and quality of care. However, the proposed rule would undoubtedly result in a dramatic reduction of the ability of hospital laboratories to provide high quality laboratory services to the patients they serve through outsourcing of testing and shrinkage of local test menus. This would result in decreased access to testing, substantially degraded timeliness of testing in the acute care setting, and decreased innovation and tailoring of testing to the needs of local patient populations and clinical programs. As such, the quality and safety of laboratory testing would be severely compromised, thus creating the opposite effect from that desired by the FDA.
- Clinical laboratories are at present one of, if not the most closely regulated area of healthcare by the Department of Health and Human Services through the Code of Federal Regulations Section 493.1253 (excerpted below in the BLUE box). Under this framework, LDTs are subjected to stringent analytic and clinical validation protocols prior to being deployed for clinical care. As a

consequence of decades of operating under these regulations, clinical laboratories are culturally constituted to be highly focused on quality and patient safety. While there are undoubtedly opportunities to improve the safety of laboratory testing, the proposed rule is far too blunt an instrument, and would result in many unintended consequences.

- The FDA's proposed rule does not adequately assess the number of tests that would fall into this category and, therefore, does not provide a realistic plan or budget for regulating LDTs.
- The costs of this program would be absorbed by hospitals, health systems, and independent laboratories that are already under substantial financial stress. Ultimately, increased costs would likely be passed on to patients.
- The severe realignment and disruption in the current paradigms of the provision of laboratory services would likely result in fewer pathology and laboratory medicine trainees, further exacerbating workforce shortages and degrading the expertise, quality and timeliness of care provided to our patients.

We urge you to respond promptly to meet the published deadline (11:59 p.m. Eastern on December 4, 2023). Based on previous experience with FDA comment periods, the announcement of an extension is likely to come within 24 hours of the original deadline. Your attention to this important matter will be greatly appreciated by your colleagues and the patients and communities you serve. **Once submitted to the Federal Register, please also send your final comments to lhowell@apcprods.org.**

**Excerpt from the Code of Federal Regulations Sec. 493.1253:**

Each laboratory that 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…), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable: accuracy, precision, analytical sensitivity, analytical specificity to include interfering substances, reportable range of test results for the test system, reference intervals (normal values), and any other performance characteristics required for test performance. HHS will establish a Clinical Laboratory Improvement Advisory Committee to advise and make recommendations on technical and scientific aspects of the provisions of this part 493.

**Excerpt from attachment #1 prepared in July 2022 by AAMC:**

Differentiating Academic Medical Center (AMC) Clinical Labs

Clinical labs in AMCs have several unique characteristics that differentiate them from other types of labs that develop and manufacture LDTs, or in vitro clinical tests. These factors were a large part of why the FDA was comfortable with the development and provision of LDTs in AMCs without FDA regulation for many years. Any revised regulatory framework must include as one goal a recognition that an overly burdensome system to review LDTs could greatly slow the rate of clinical innovation that is critical to keeping our health care system at the forefront of discovery, providing quality care to patients, and responding quickly to emerging public health risks. The extensive time commitment and the economic impact of institutional compliance with the proposed new regulatory framework for currently administered and newly developed LDTs would be untenable, given the time and cost of guiding even a single test through the FDA premarket approval process. This cost would necessarily lead to institutional decisions that could limit patient access to innovative and targeted diagnostic tests.

Key characteristics of academic clinical laboratories (ACLs):

• The ACL is an integrated and integral aspect of an academic institution, which provides direct patient medical care.

• The primary role of the lab is to provide testing and interpretation for the benefit of the patients and clinicians in an affiliated hospital or academic health center as a part of the treatment decision-making process.

• ACLs have been certified by the Centers for Medicare & Medicaid Services through the CLIA (Clinical Laboratory Improvement Amendments) program to conduct high-complexity tests.

**Excerpt from the FDA's proposed rule:**

In addition, FDA is aware that some AMCs have claimed that their laboratories operate under unique circumstances (such as being integrated into direct patient care) and therefore their tests should be treated differently than tests manufactured by other laboratories. Although FDA is not aware of an established definition of an AMC laboratory, one possible description is: a laboratory for which a certificate is in effect under CLIA and that meets the requirements under CLIA to perform tests of high-complexity; that is part of an accredited public or nonprofit private AMC that has a medical residency training program or fellowship program related to test development, application, and interpretation; and that is integrated into the direct medical care for a patient, including specimen collection, testing, interaction with the treating provider, and, as appropriate, patient treatment based on the test, all at the same physical location.

FDA seeks comments on the following:

• What are the characteristics of AMC laboratories? Do the characteristics included above accurately describe AMC laboratories and in fact distinguish them from other laboratories?

• Should FDA continue the general enforcement discretion approach with respect to any requirements, such as premarket review requirements, for tests manufactured by AMC laboratories?

• If FDA should continue the general enforcement discretion approach with respect to any requirements, such as premarket review requirements, for tests manufactured by AMC laboratories, are there any additional considerations that should be taken into account with respect to this approach, for example, whether an FDA cleared or approved test is available for the same intended use as the test manufactured by an AMC laboratory? Please provide a rationale and other information (e.g., data) to support any additional considerations.

• If FDA should have a different policy for AMC laboratories, what would be the public health rationale to support such a policy? For example, if integration of an AMC laboratory into direct patient care is included as a basis for a different policy, please include a public health rationale when explaining why and how such integration supports the different policy, and how integration could ensure that there is a reasonable assurance of IVD safety and effectiveness.

• If FDA should have a different policy for AMC laboratories, is there evidence to support such a policy?

Sincerely,

Michael Laposata, MD, PhD
President, Association of Pathology Chairs
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# The Regulation of Laboratory-Developed Tests

## AAMC Position

The AAMC affirms that it is essential for laboratory-developed tests (LDTs) to be accurate and clinically valid in their use as diagnostics informing treatment decisions for patients. However, we share our academic medical center (AMC), teaching hospital, and physician faculty's concerns that the **regulation of LDTs by the U.S. Food and Drug Administration (FDA) as proposed in the Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2022 and incorporated into the Senate Health, Education, Labor, and Pensions (HELP) Committee's FDA Safety and Landmark Advancements (FDASLA) Act would interfere with delivering innovative, cutting-edge medical care, negatively impact patients, and mire the development of critical new tests in a costly and laborious regulatory process.** The AAMC joined over 100 stakeholders in a June 16 letter reiterating these concerns, and sent its own letter on June 2.

As the AAMC has consistently communicated, AMCs, teaching hospitals, and the faculty physicians that are performing LDTs every day on the front line of patient care are best able to determine the best way to treat patients with important information gleaned from clinically validated, well-proven, and carefully tailored diagnostic tests. The FDA should be working in concert with academic medicine to encourage safe innovation in patient care, not stifle it.

As the regulation of in vitro clinical tests is debated in Congress, the AAMC is engaged with many stakeholders and continues to advocate to allow for the valuable and critical use of LDTs in the practice of medicine. With the input of many AAMC-member institutions who are deeply engaged in the development and provision of LDTs for the benefit of patients across the nation, the AAMC has identified key issues that must be addressed in any proposed or implemented regulation of LDTs.

## Key Messages for Congress's Consideration of the VALID Act as Part of the FDASLA

### *Differentiating Academic Medical Center Clinical Labs*

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Key characteristics of academic clinical laboratories (ACLs):

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- The primary role of the lab is to provide testing and interpretation for the benefit of the patients and clinicians in an affiliated hospital or academic health center as a part of the treatment decision-making process.
- ACLs have been certified by the Centers for Medicare & Medicaid Services through the CLIA (Clinical Laboratory Improvement Amendments) program to conduct high-complexity tests.

## Requests

Given AMC labs integration of the test development and administration into the continuum of patient care, the many other safeguards for patients that such labs are already subject to, and the FDA's retention of the ability to investigate and remove any test from the market regardless of the entity that develops it, **we urge Congress to exempt these "academic clinical laboratories" from the revised oversight framework presented in the FDASLA**. Short of that, lessening the burden on academic labs by addressing several provisions in the FDASLA would make these new regulations less likely to decrease the number of available tests for patient care and potentially negatively impact patients' health.

The most onerous and resource-intensive aspects of the FDASLA could be diminished without increased risk to patients or access to care by making the following changes applicable only to labs that are designated as "academic clinical laboratories" (ACLs):

- Exclude ACLs from the requirement to proactively list all tests that are to be grandfathered under [§587]. Instead, such labs should be prepared to present evidence of use of the test prior to enactment should a question arise about whether a test was properly included in this exemption.
- Have every test developed by an ACL be designated as low-risk and not subject to the additional requirements for high-risk tests [§587(9)]. This would acknowledge the risk-mitigating factors that arise from additional oversight, expertise, and integration into clinical care that ACLs demonstrate, aspects that are wholly different from commercial or reference labs.
- When a test is grandfathered, exempt from premarket review through a technology certification, or approved through premarket review if that test is developed and administered by an ACL, any changes to the type of specimen used for the test would not be considered a modification which would cause it to be treated as a new test [§587C(a)(6)].
- Expand custom/low volume tests exempt categories to include <100 tests annually (instead of five).

## Additional Background

For many years, the development and provision of LDTs in the context of clinical care was deemed by the FDA and by academic labs to be different enough from the tests provided by commercial labs to not require additional oversight and regulation. In October 2014, the FDA released draft guidance on proposed oversight of LDTs, and in vitro diagnostic tests, both of which are designed and used by a single laboratory. The LDTs offered by clinical labs at academic medical centers were not regulated by the FDA through the existing device regulations, but many would have been subject to this regulatory oversight under the proposed guidance and subsequent proposed legislation. According to the FDA, the purpose of the revised framework was to give the FDA oversight of LDTs "based on risk to patients rather than whether they were made by a conventional manufacturer or a single laboratory." In this structure, LDTs designated as higher-risk, including companion diagnostics and LDTs used to inform treatment decisions, would be reviewed by the FDA through the existing pre-market review process used for devices. The FDA proposed to continue to use its enforcement discretion and not require the same process for certain LDTs, including those deemed to be low-risk and those used for rare diseases.

In response to concerns raised by the academic medicine community and other stakeholders, the FDA did not finalize the draft guidance, and subsequently Congress drafted and introduced several versions of proposed legislation to require FDA oversight of LDTs, with the most recent bill, the VALID Act, being incorporated into the Senate HELP Committee's draft FDA user fee reauthorization text, the FDASLA Act of 2022.

## AAMC Government Relations Contacts

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