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December 4, 2023

Robert Califf, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: Medical Devices; Laboratory Developed Tests (Docket No. FDA-2023-N-2177); 88 FR 68006

Submitted electronically at <https://www.regulations.gov>

Dear Commissioner Califf,

The Association of American Medical Colleges (AAMC) appreciates the opportunity to provide feedback to the Food and Drug Administration (FDA) on a proposed rule to regulate laboratory developed tests (LDTs) and the accompanying proposed enforcement policy.

The AAMC is a nonprofit association dedicated to improving the health of people everywhere through medical education, health care, medical research, and community collaborations. Its members are all 158 U.S. medical schools accredited by the Liaison Committee on Medical Education; 12 accredited Canadian medical schools; approximately 400 academic health systems and teaching hospitals, including Department of Veterans Affairs medical centers; and more than 70 academic societies. Through these institutions and organizations, the AAMC leads and serves America's medical schools, academic health systems and teaching hospitals, and the millions of individuals across academic medicine, including more than 193,000 full-time faculty members, 96,000 medical students, 153,000 resident physicians, and 60,000 graduate students and postdoctoral researchers in the biomedical sciences. Following a 2022 merger, the Alliance of Academic Health Centers and the Alliance of Academic Health Centers International broadened participation in the AAMC by U.S. and international academic health centers.

We share the FDA's desire to ensure that LDTs provide accurate, timely diagnostic information so that providers, with patients and their families, can best determine a course of treatment. That is precisely the goal, the mandate, and the experience of the academic medical centers that have successfully developed LDTs for years to guide decisions about treatment plans. The AAMC is concerned that the FDA's proposed enforcement policy would have an immediate and detrimental effect on the ability of academic medical centers and their physician faculty to provide specialized and patient-centric medical care.

Diagnostic testing is a critical element of medical decision-making. In many cases, commercially available diagnostic tests can provide a health care provider with sufficient information to recommend a treatment plan. The patients who come to academic medical centers, however, often require more tailored, specialized, or specific diagnostic tools. This is where the unique value of laboratory developed tests comes into play. These tests, when created in an academic laboratory that is certified for high-complexity testing, meet the needs of patients and providers and fill gaps where commercial products do not, and will never exist. It is only because of these LDTs that many of these patients can receive accurate diagnoses and life-changing medical treatment, including those with rare diseases, genetic and metabolic disorders, emerging infectious agents, pediatric illnesses, and cancer-causing gene mutations. At academic medical centers, the development of LDTs is exacting, rigorous, resource-intensive, and an essential component of patient care. While LDTs manufactured outside of academic medical centers have been identified with consumer harm and inaccurate results, a federal response that makes safe, accurate, and needed LDTs unavailable to patients does not promote public health and welfare. We are concerned that this proposal establishes a broad, disruptive oversight mechanism that will hinder the ability of academic medical centers to provide care to patients who need it most.

As further described below, these are the AAMC's primary concerns with the FDA's proposal:

1. The FDA has not established that this proposed oversight mechanism is warranted with respect to LDTs created at academic medical centers, which constitute a unique subset of LDTs as a result of the highly regulated environment in which they are created and their uses with patients for whom commercially available tests are insufficient. The FDA's mandate to protect the public health would be better served by a targeted enforcement policy to address the concerning reports related to in vitro diagnostic tests (IVDs) manufactured outside of academic medical centers.
2. The large volume of tests that would need to be submitted to and reviewed by the FDA would strain institutional resources and create a regulatory bottleneck that would prevent the agency from addressing identified problems with direct-to-consumer and other LDTs developed purely for commercial purposes, decreasing the FDA's ability to respond to the public health threat the agency has identified.
3. As a result of the proposed change in the FDA's approach to all LDTs, each academic medical center would be forced to make decisions about how many applications to the FDA the institution would be able to support and which tests would be abandoned or not developed, to the detriment of the patients that could benefit from them.
4. Rather than spur innovation through competition as asserted, the enforcement policy would instead result in tests that are never developed or can no longer be used. This threat to patient care is neither addressed in the proposal nor taken into account in the cost benefit analysis in the proposal.

Accordingly, we urge the FDA to maintain its enforcement discretion for tests that are developed in the highly regulated, specialized academic medical center environment to allow the agency to focus on those tests being marketed directly to patients without the safeguards and oversight which are already an integral part of LDT development at academic medical centers. Prior to embarking on a comprehensive enforcement policy, the FDA should: 1) prioritize collecting data about the volume of LDTs that would be impacted and identifying those tests that present the highest risk to the public as a result of the environment in which they are developed and used, 2) pilot this new regulatory approach, and 3) use the resulting data on cost, time for review, and percent of applications rejected to develop a new proposal for future enforcement activities.

We commend to the FDA the many comment letters submitted by academic medical centers in response to this proposed rule and enforcement policy. We are keenly aware that these institutions are committed to addressing patient needs through the development and use of validated, accurate diagnostic tests. Many of these letters also respond to the FDA's request for data by providing detailed institution-specific information about the number of tests that would be affected, the long history of successful use of LDTs, the substantial cost of this proposal to an academic laboratory, and the tangible impact to patients that would result when the institution is forced to abandon certain tests and pass along the increased costs of remaining tests to patients and insurers.

The academic medical center laboratory environment provides a higher level of oversight, regulation, engagement between laboratory and clinician, expertise, and focus on specific patient need than does commercial manufacturers of LDTs and thus warrants continued general enforcement discretion with respect to LDTs developed at academic laboratories.

The AAMC agrees that patients should never be put in a position to make life-changing medical decisions based on tests that may not be accurate or validated. We recognize that people have been harmed through the types of tests the FDA cites in the proposal, including direct-to-consumer prenatal genetic screening tests, and that those tests should be a priority of the FDA to identify and regulate. These are not representative or indicative of the tests that are being developed at academic medical centers. The LDTs developed at academic medical centers seek to address pressing medical needs and complicated diagnosis for which their academic physicians require more information than can be gleaned from standard or commercially available tests. They have been consistently and successfully used to guide patient treatment decision-making. Academic clinical laboratories are highly regulated entities, and LDTs are developed in an environment that is designed to provide providers and patients confidence that the diagnostic tests are accurate, necessary, and thoroughly validated. These factors, taken in concert, provide sufficient risk mitigation to warrant the FDA's continued general enforcement discretion with respect to all LDTs at academic medical centers.

Academic medical center laboratories are certified to perform high-complexity testing by the Centers for Medicare & Medicaid Services through the Clinical Laboratory Improvements Act of 1988 (CLIA). CLIA certification requires that laboratories demonstrate analytical validity of the tests they develop (i.e., that the test demonstrates accuracy, precision, analytical sensitivity, and analytical specificity). In the proposed policy, the FDA correctly notes that this CLIA certification does not require demonstration of clinical validity for individual tests (i.e., how well the test predicts the risk of or presence of a disease or condition). However, CLIA is not the only set of standards and oversight to which the academic laboratory is subject. In addition to CLIA, many labs are further accredited or regulated through state mechanisms such as the New York State Department of Health Clinical Laboratory Evaluation Program (CLEP) or the validation programs through the Veterans Health Administration. Further, the close connection between the clinical pathologists developing the tests and the care providers further validates the alignment between diagnostic results and clinical presentation. As a result of this connection through the academic medical center, clinicians can provide real-time feedback to the LDT developers on test performance and outcomes. This is in contrast to the feedback process between health care providers and commercial labs, in which concerns about test accuracy or validity may be routed through quality assurance or customer service departments. AAMC members have reported delays of many months between first expressing concern about a commercial test and receiving notification that the test needed to be modified or was no longer in use as a result of feedback from institutions.

The FDA has provided for consideration a definition of “academic medical center” for the purposes of considering continuing enforcement discretion at these entities. While the AAMC is fully supportive of the FDA's using general enforcement discretion with respect to tests at academic medical centers, the definition provided is problematic as it would tend to arbitrarily exclude certain organizations that are unquestionably academic medical centers for which general enforcement discretion would be appropriate. The proposed definition 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.”

Many of the characteristics of an academic medical center are alluded to in this definition. The AAMC suggests that the following aspects of the definition require revision:

- **“including specimen collection, testing, interaction with the treating provider, and, as appropriate, patient treatment based on the test, all at the same physical**

location”: The integration of the test-developing clinical lab into the arc of patient care through affiliation through a single system is essential to identifying an LDT for an academic medical center. However, the requirement that specimen collection, testing, interaction with the treating provider, and even patient treatment based on the test take place at the same physical location fails to recognize the reality of how these institutions are connected, situated, and treat patients. The complexity of an academic medical center means that the physical location of a building is not necessarily an indication of the level of connectivity between two departments or facilities. Increases in clinical space needs, populations, and the value of real estate force academic institutions to take advantage of available space and opportunities. It would not be unusual for a clinical lab, a treatment site, and a specimen collection site to be physically distinct from each other. These departments or facilities may be every bit as connected as when entire departments are “down the hall” from each other. The activities at an academic hospital related to the development and deployment of LDTs could be within a hospital center, in a basic science department at the affiliated school of medicine, or in a free-standing building. The definition of academic medical center, if used for enforcement discretion, should capture an understanding of a closely affiliated components of one system rather than a single physical location.

- **“a medical residency training program or fellowship program related to test development, application, and interpretation”:** The AAMC agrees that the presence of a residency training program is a defining hallmark of an academic medical center. The definition, however, suggests that the enforcement discretion should hinge on having a specific residency program “related to test development.” Unless this is intended to imply that the institution has a pathology residency program, do not see the need for this descriptor. The existence of a residency program in any specialty indicates an academic medical training program. We would not want to suggest that the FDA enforcement discretion should be employed because an institution has a program in which to train individuals to create LDTs. Instead, we would suggest that any definition simply indicate that the academic medical center “has a medical residency training program.”

The FDA has asked whether additional considerations should be taken into account with respect to LDTs at academic medical center laboratories, including considering whether there is an existing test available for the same intended use. These tests are pursued by academic labs specifically because the health care provider does not have access to a sufficient test to help guide a diagnosis and treatment plan. Diagnoses that can be made with readily available commercial tests are already being used. The LDTs from academic medical centers include those for rare or orphan diseases, emerging infectious diseases, complex conditions for which different treatment options would be employed depending on a diagnostic output, pediatric patients for whom there is no available test or guidance as to how an available test made for adults should be

used, or patients for whom available diagnostics failed to provide key information for treatment decisions. The existence of a test “for the same intended use” does not alone indicate whether the existing test would be appropriate for that patient and may not be accessible to a patient from another institution.

The large volume of LDTs would make implementation of the proposed enforcement policy infeasible for both the FDA and academic medical centers, ultimately to the detriment of patients and to the FDA’s stated goal of addressing identified urgent public health threats.

As proposed, the number of LDT applications that would need to be submitted in the 4 years after the policy is finalized far exceeds the capabilities of the academic medical center community, both collectively and per institution. As has been compellingly demonstrated in letters from individual institutions, the volume of tests for which an application would be required would very quickly outstrip the resources expertise and personnel at academic medical centers, few of which have designated staff for FDA regulatory submissions. The compliance mechanisms at these academic centers are extensive, focused on the work needed for the robust accreditation of labs through CLIA, hospital accreditation through the Joint Commission, many other regulatory and accreditation bodies, and the exacting standards the labs use to validate their own tests, using feedback and expertise from the academic health care providers. Even though the FDA has suggested that laboratories could continue to deploy LDTs while awaiting FDA review, the rate of submission required would quickly overwhelm most academic institutions, with the result that some of those tests would no longer be offered.

The AAMC also shares the concerns expressed by many others that the FDA itself does not have the resources to be able to undertake a timely review of the vast numbers of applications that would be required as a result of the proposed policy. A conservative estimate of the number of tests that would be submitted in the first year alone would be many times the total number of medical device approvals that FDA typically completes in a year, with an increasing number of complex applications in subsequent years. Without a substantial increase in staff and review capacity at the FDA, the successful and meaningful implementation of this policy would be thwarted, and the true expense and burden of the program would be difficult to assess.

Most importantly, not only would this abrupt policy change strain the resources of both test developers and test reviewers, but the signal to noise ratio would also be minuscule; the flood of applications would hinder the agency’s ability to quickly identify those tests the FDA has already identified as providing the most risk of harm to Americans. As a result, these harmful tests might not be reviewed for years.

If the public health threat of non-validated, direct-to-consumer commercial tests that have taken advantage of the FDA’s enforcement discretion of LDTs is as great as asserted, it would be prudent for the FDA to direct its energies in these early days to identifying those tests for which

enforcement discretion is no longer appropriate. The characteristics of the tests for which AAMC suggests FDA focus its enforcement priorities align with the concerns raised by the FDA in its background justification for the policy change:

- The test is provided directly to consumers for the purpose of making health care decisions without the benefit of interpretation by a healthcare provider.
- The test is developed for commercial purposes by an entity unaffiliated with an academic medical center.

As a result of the proposed change in approach to LDTs, academic medical centers would be forced to make decisions about which FDA applications would be assembled and submitted, and which tests would instead be abandoned or not developed, to the detriment of the patients that could benefit from them.

In addition to the time and personnel needs to assemble all required regulatory submissions for tests that are existing and under development, the financial ramifications of this policy change would be prohibitive, costing institutions millions of dollars in user fees and additional costs of preparing the submissions. If implemented as proposed, the enforcement policy would devastate a system already under financial stress without a commensurate value in improved test performance. As a result, institutions would be required to do a financial analysis of their currently available LDTs and those under development to choose which are worth the further regulatory investment. Those tests that are no longer available may be those that impact a smaller number of people, are less likely to be reimbursed and thus allowing the institution to recoup its costs, or would require a more complicated submission process. These are not the criteria that academic medical centers have used to determine when there is a critical need for a test.

Rather than spur innovation through competition as asserted, the enforcement policy would instead result in tests that are never developed or can no longer be used. This threat to patient care is neither addressed in the proposal nor taken into account in the cost benefit analysis for the proposal.

The assertion that regulation of all LDTs would spur innovation and competition has been met with strong skepticism. The reason that most LDTs are developed at academic labs are because there isn't a strong identified commercial market for the test. If there were, those tests would already have been manufactured and become commercially available – and our medical centers would be using them. Especially in the context of rare diseases or pediatric tests, many of the LDTs that academic medical centers develop would never be made available.

The foreseeable result of the implementation of this policy change is a profound and immediate impact on patients. Some will not get accurate or tailored diagnostic information. Some will need

to rely on a treatment plan based on incomplete information or a diagnosis based on less specific clinical measures.

The speculative cost/benefit analysis presented in the Federal Register not only underestimates the costs to academic laboratories, but also omits the costs to patients and the health care system of missed or inaccurate diagnoses as a result of LDTs no longer available.

Considerations for the proposed enforcement strategy

Although the AAMC urges the FDA to use general enforcement discretion for all academic medical center LDTs for the research detailed above, we note that should the FDA's enforcement strategy proceed as proposed there are several aspects of the plan that would make implementation impractical or entirely infeasible for academic medical centers:

Low volume and rare disease tests: Previous proposed enforcement policies have made broad exceptions for low volume tests, such as those for pediatric diagnoses for which an existing adult test is not appropriate, and those for rare diseases. As a result of the financial burdens of the proposed policy change, these tests would be unlikely to remain available and should not be included in FDA enforcement activity.

Grandfathering: There is no compelling interest for FDA to require the broad submission of tests that have been used successfully for many years and present low or moderate risk to patients. Under any enforcement policy, those tests that are established at institutions demonstrating the mitigating factors described above should be grandfathered in and exempt from all premarket review requirements.

Duplicative oversight: As described above, in addition to the rigorous laboratory oversight represented by CLIA certification, academic medical center laboratories have additional layers of certification, accreditation, and oversight as a result of state programs such as the New York CLEP review, and those from VHA, accrediting bodies, and specialty-specific requirements. An enforcement policy that does not take into account all additional oversight mechanisms for LDTs developed at academic medical centers would be duplicative, burdensome, and expensive without any meaningful impact on public health or patient safety.

Implementation timeline: The AAMC's member institutions have widely reported that the 4-year implementation timeline would be impossible to implement, even with a substantial influx of resources to address the requirements. We note that this proposed timeline is less than half of the 9 years FDA originally proposed for implementation in its 2014 guidance.

In sum, the FDA has already identified the specific attributes of tests that pose a public health threat and require additional oversight. Those tests are not coming from the highly regulated, patient-focused academic clinical labs. The agency should prioritize for regulation tests created for commercial purposes, provided to consumers outside the highly regulated environment of an academic medical center, and marketed directly to consumers with the promise of being able to make critical health care decisions without the benefit of interpretation and expertise of a healthcare provider. The cost benefit analysis provided is both highly speculative and importantly incomplete. Rather than spur innovation or competition in a way that will increase the availability of critical diagnostic tests, the approach as proposed will unquestionably limit the diagnostic tools available to academic clinicians when making difficult and life changing recommendations to their patients facing serious illnesses. With limited available resources, institutions will be forced to make decisions about which tests to develop or continue using based on a financial analysis, not clinical need. Our patients and their families expect more and deserve better.

The AAMC is committed to improving the health of people everywhere. Those who seek care at academic medical centers have high expectations that our members proudly and consistently deliver, including ensuring that their health care providers have access to accurate and timely diagnostic tests to guide treatment decisions. We remain committed to working with FDA and all other interested groups to address threats to public health while delivering high quality care to patients. Please feel free to contact me directly with any questions about these comments.

Sincerely,

A handwritten signature in blue ink that reads "Heather H. Pierce". The signature is fluid and cursive, with the first name being the most prominent.

Heather H. Pierce, JD, MPH
Acting Chief Scientific Officer
Senior Director for Science Policy and Regulatory Counsel

cc: David J. Skorton, MD, AAMC President and Chief Executive Officer