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February 2, 2015

Margaret Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0360 for Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

Dear Commissioner Hamburg:

The Association of American Medical Colleges (AAMC) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance regarding the regulation of laboratory developed tests (LDTs), a subset of *in vitro* diagnostic devices. The AAMC is a not-for-profit association representing all 141 accredited U.S. allopathic medical schools, nearly 400 major teaching hospitals and health systems, including 51 Department of Veterans Affairs medical centers, and 90 academic and scientific societies. Through these institutions, the AAMC represents 148,000 faculty members, 83,000 medical students, 115,000 resident physicians, and thousands of graduate students and post-doctoral trainees in the biomedical sciences.

The AAMC shares the FDA's interest in assuring clinical validity and accuracy of LDTs for diagnostic and treatment decisions. We must collectively ensure that the regulation of LDTs as proposed in this guidance does not interfere with a vital area of medical practice, negatively impact patients across the country, or create a burdensome, laborious process that could stifle innovations to aid in the treatment of rare and complex diseases.

Accordingly, we urge the FDA to consider carefully the impact of this proposed guidance as described in the detailed comment letters from the academic medical centers and teaching hospitals that are performing LDTs each day to inform critical patient care decisions. It is these institutions on the front line of patient care that are best able to define the impact on their own institutions and their ability to treat patients with important information gleaned from clinically validated, well-proven, and carefully tailored diagnostic tests. In light of the President's new initiative on precision medicine, the FDA should be working in concert with academic medicine to encourage innovation in patient care, not stifle it. In these comments, we recommend that the FDA consider how best to accomplish the goals of the regulations without the deleterious effect predicted by the physicians and institutions that regularly perform these tests.

The number of tests and patients that would be impacted is significant. It has been estimated that as many as 100,000 LDTs are used in clinical practice today. Many of these LDTs are offered to patients at some of the nation's largest academic medical centers. As one example, the Mayo Clinic currently has over 1,600 LDTs available to patients and, in the past 6 years, has performed over 2.5 million of these LDTs for Mayo Clinic patients and 19 million LDTs for patients outside of the Mayo Clinic through the Mayo Medical Laboratories.¹

The regulatory framework as described in the proposed guidance would greatly slow the rate of clinical innovation that is critical to keeping our healthcare system vital, providing care to patients, and responding quickly to emerging public health risks. Clinical laboratories in academic medical centers are often the most innovative early-adopters of new technology. Similarly, many of our institutions are concerned what impact intent of use guidelines will have on consultation relationships with the laboratory in an academic medicine setting. Advances in laboratory medicine have fundamentally changed our understanding of the mechanisms of disease, enabling physicians to diagnose conditions more precisely, detect the onset of disease earlier, target patient treatments more effectively, and would not have been possible without the current regulatory framework governing LDTs.

The ability of laboratories to develop custom diagnostic tests has been critical to the growth of personalized medicine and keeping pace with the changing face of disease to best serve patients and clinicians. Often in the academic setting, LDTs are not distributed as kits, but ordered electronically with the intended use unstated. If proposed regulations restrict the off-label use of LDTs, physicians may abstain from ordering their testing through the lab. Furthermore, stringent guidelines regarding intended use could undermine the clinical knowledge and unique partnership between the laboratory and the ordering physician.

LDTs have long addressed emerging public health risks. Our academic medical centers are often called upon to meet the needs of small patient populations with rare diseases or conditions and are often leaders in the public health response to infectious diseases. As was so vividly demonstrated during the recent Ebola virus threat, the timely and immediate response by medical center laboratories is critical to the welfare of patients and the public health.

LDTs are often innovative or low-volume tests whose speed of adoption has out-paced the ability of commercial IVD manufacturers to plan and submit formal clinical trials that would be required for FDA approval for marketing. These tests are often developed and performed in a single academic hospital laboratory to support hospital clinicians, rather than based on external commercial strategies and marketing programs. The rapid development and performance is the advantage of using LDTs in academic medical centers that are equipped to address local demands to test for rare diseases, to respond to interventions that are applied in narrow settings, and to detect pathogens or environmental toxins unique to a specific environment. If the FDA employs a premarket approval process, the original intent of LDTs will be devastated.

The cost of institutional compliance with a new regulatory framework for currently administered and newly developed LDTs could limit patient access to innovative and targeted diagnostic tests. The AAMC and our members are concerned about the potential impact on the viability of academic and community based laboratories that perform LDTs if the

¹ See the comment letter from Mayo Clinic for additional details.

FDA guidance is implemented as currently drafted. Specifically, given that most large academic hospital labs perform anywhere from dozens to over a thousand different LDTs, the regulatory infrastructure within the hospital and at the FDA could be prohibitively expensive. FDA-related expenses at the level of premarket approval would mount quickly to millions of dollars. Moreover, we anticipate that such regulation would not reduce healthcare costs, but rather significantly increase costs. Many LDTs developed from general purpose reagents are cost-effective alternatives to FDA-approved or cleared reagents.

Despite the large number of tests that exist, the number of patients who benefit from a single test could be small as the tests become more tailored to a limited number of people. Thus, the calculation of whether to obtain FDA approval through this proposed framework for any one test may lead laboratories within academic medical centers to determine that the increased cost for a low-volume test is not worth pursuing. If the FDA were to require clearance or approval for all LDTs, laboratories may be unable to continue offering many of them. Some testing currently performed at laboratories as LDTs will never generate the financial returns to justify the costs of obtaining FDA clearance or approval, or to implement the infrastructure needed for the proposed notification process. We suspect that critical testing would be unavailable in the time between development of a new test and FDA approval and authorization of use.

The FDA should broaden the categories of LDTs and situations under which it will exercise its enforcement jurisdiction. As many have commented in public hearings on this topic and in written comments, the scope of exceptions to the draft guidance are limited. Although the exceptions for *traditional LDTs*, *unmet needs*, and *rare diseases* are meaningful in principle, the narrow definitions and applications make it unlikely that the described carve-outs will have the intended effect. Limiting “traditional LDTs” to those tests interpreted without automated instruments or software seems short-sighted, and may create an incentive not to take advantage of the latest technology available to ensure that a test still fits in this limited scope. The guidance for “unmet needs” is not clear, and our member institutions report not understanding when this enforcement discretion would be exercised. Finally, as many others have noted, defining “rare diseases” based on the number of tests performed, and not by the prevalence of the disease itself limits the utility of this exception and may unduly limit the number of these critical LDTs developed or performed.

Some of AAMC’s member institutions, including the Mayo Clinic, have suggested including a grandfathering provision for LDTs developed and offered pre-2010. This exclusion would not require laboratories to provide notification or submission of tests implemented prior to 2010. The provision could exclude those LDTs that reasonably would fall under the FDA’s proposed definition of a high-risk LDT. Having to notify the FDA about LDTs offered pre-2010 would waste limited resources for both the clinical laboratory as well as the FDA, and we suggest the FDA consider taking such an approach.

Currently, the provision of LDTs through clinical laboratories are already regulated through a host of mechanisms, including the Clinical Laboratory Improvement Amendments (CLIA), accreditation standards, the regulation of the practice of medicine, and state laws that apply to clinical laboratories. The FDA should take into account the web of mechanisms that already serve to ensure that patients and physicians benefit from accurate and validated test results.

The AAMC is grateful for the opportunity to comment on this draft guidance. We look forward to working in collaboration with our member institutions and the FDA to develop a framework that ensures tests used to make important treatment decisions for patients are reliable and accurate, but also fosters innovation in the delivery of healthcare without the likely unintended consequences this current draft guidance would cause. We would be happy to provide any further assistance in this process. Please feel free to contact Heather Pierce, Senior Director for Science Policy and Regulatory Counsel at hpierce@aamc.org or (202) 478-9926 with any questions.

Sincerely,

A handwritten signature in cursive script that reads "Ann Bonham".

Ann C. Bonham, Ph.D.
Chief Scientific Officer