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Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1601
Rockville, MD 20852

RE: Docket No. FDA-2011-D-0360: Framework for Regulatory Oversight of Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories.

Dear Dr. Hamburg:

On behalf of our nearly 5,000 member hospitals, health systems and other health care organizations, and our 43,000 individual members, the American Hospital Association (AHA) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) and related guidance, which would apply medical device regulations to clinical laboratory services.

Many hospitals and health care systems have LDTs, particularly larger hospitals and academic medical centers. LDTs are diagnostic tests that are not commercially distributed to other laboratories but, instead, are developed, validated and performed in-house by individual laboratories. These range from routine tests such as blood counts to more complex molecular and genetic tests in cancer, heart disease, and rare and infectious diseases. LDTs provide timely patient access to accurate and high-quality testing for many conditions for which no commercial test exists or where an existing test does not meet current clinical needs. They provide physicians with important clinical information to diagnose and treat patients and are critical in the practice of all areas of medicine. These tests are typically developed at the request of, and in close collaboration with, clinical caregivers.

The AHA is concerned that the FDA's draft framework, while well-intentioned, is inappropriate and will lead to a loss of patient access to many critical tests. Given the value of these tests to caregivers and patients, the AHA believes that any framework for regulatory oversight of LDTs must ensure that the technological and clinical innovation that is essential to the development of LDTs remains unrestricted; that the quality and reliability of LDTs are maintained at the highest levels possible; and that LDTs continue to be widely accessible to patients. In contrast, we believe the draft framework, instead, will cause confusion and delays

that will hinder the achievement of these goals, ultimately preventing hospital and health care system laboratories from continuing to develop cutting-edge LDTs in response to immediate clinical care needs.

Rather than regulating LDTs itself, the AHA strongly urges the FDA to allow the regulation of LDTs to remain under the Clinical Laboratory Improvement Amendments (CLIA) regulations and the deemed accreditation bodies. However, we acknowledge that this current regulatory oversight mechanism has not kept pace with the rapid changes in medical technology and knowledge in laboratory medicine. Therefore, there is a need to modernize and enhance the oversight process and requirements under CLIA and to strengthen the role of third-party accreditors. We stand ready to work with the FDA, the federal agencies that oversee CLIA and other stakeholders to make these improvements.

If the FDA nevertheless intends to impose its device regulations on LDTs, we urge the agency to withdraw the draft guidance and instead issue new proposed requirements through notice-and-comment rulemaking. This is not only required under law, but doing so would provide essential protections for hospitals and other regulated parties.

CLIA SHOULD BE ENHANCED AND MODERNIZED TO ADDRESS ANY GAPS IN OVERSIGHT

LDTs are Not Devices and Should Not be Regulated as Such. In its rationale for establishing regulatory oversight for LDTs, the FDA describes these testing services as a subset of in vitro diagnostic devices (IVDs). Therefore, the FDA reasons it should begin applying its device regulations to certain categories of LDTs. However, LDTs are fundamentally different than commercially available IVD kits and should not be regulated as such. Unlike mass-produced commercial IVD test kits that are shipped by manufacturers around the country, the development of LDTs does not require manufacturing of supplies, and all testing is done in the same laboratory that initially developed the LDT as part of the laboratory physician's practice of medicine. In addition, once a commercial kit is shipped, the manufacturer loses control of all aspects of the testing that follows, including how the test is conducted, which patients are tested and how the test results are communicated. By contrast, LDTs remain within the control of the laboratory physician from test design to the communication of test results to the ordering physician. Further, while commercial kits are designed for use with a "standard" patient, LDTs are selected for each individual patient based on their condition, in consultation with their treating physician. In short, LDTs are services offered by laboratory physicians practicing medicine and, as such, they are outside of the FDA's scope of authority and should not be subject to the FDA's rigid regulatory structure for mass-produced commercial kits.

Current Regulatory Oversight of LDTs by CLIA is Appropriate. **The AHA supports keeping the current regulatory model under CLIA and overseen by Centers for Medicare & Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC) as the primary means for regulating LDTs. Involvement by another federal regulatory body such as the FDA is unnecessary, duplicative and potentially conflicting.**

The FDA has cited concerns about the quality of LDTs as the primary impetus for developing the risk-based framework for regulatory oversight, asserting that testing errors have caused patient

harm. The agency asserts that applying additional oversight will help ensure safety and quality. However, we are unaware of, and the agency has not offered evidence of, patient harm that would justify imposing broad new and costly regulatory requirements that will most assuredly harm patients, who will subsequently lose access to needed testing services.

In addition, LDTs, and the laboratories and personnel that develop and perform them, are already highly regulated under a three-part framework consisting of federal regulations under the CLIA, state laws and accreditation by deemed authorities, such as the College of American Pathologists (CAP), and The Joint Commission. For example, CLIA subjects LDTs to strict personnel, quality control and proficiency testing standards. In addition, CLIA labs must document the analytic validity of LDTs, including determinations of accuracy, reproducibility and other test-performance characteristics, in order to assure reliable and safe test results. Such information is regularly made available to inspectors. Most labs conducting LDTs are subject to state and private sector oversight as well. For instance, New York State requires labs to document analytic and clinical validity prior to introducing a test. Similarly, CAP requires that testing facilities demonstrate the analytic validity of LDTs and document clinical validation.

This existing framework ensures that clinical laboratory physicians and scientists perform careful inspections of laboratory facilities, exhaustive review of test protocols and validation, and continually monitor laboratory performance. Extensive validation and continuous monitoring ensure the performance, quality and reliability of diagnostic services, while still allowing laboratories the flexibility to rapidly develop and validate modifications to laboratory tests and more quickly adopt new scientific knowledge and respond to unmet public health needs.

Furthermore, we are concerned that the FDA lacks the resources to effectively manage this entirely new area of regulation. There are tens of thousands of LDTs in existence today, with hundreds of new tests created every year. In contrast, in 2013, the FDA approved 23 pre-market approval applications. Clearing or approving all of the existing LDTs for use clearly would be an enormous undertaking, and we have serious concerns about the FDA's ability to handle this additional workload.

Areas of Regulatory Overlap and Gaps in Oversight Should be Resolved through CLIA Modernization. As the FDA points out in its draft guidance, there are important areas of FDA oversight that are not included in the CLIA law and regulations, such as clinical validation, design controls and adverse event reporting. **The AHA believes that, instead of subjecting clinical laboratories to multiple oversight agencies, a better approach would be to modernize and enhance CLIA.** This should include adding new areas of oversight that are needed to ensure the safety and effectiveness of LDTs and strengthening the role of third-party accreditors.

The AHA urges CMS, CDC and the FDA to engage stakeholders in a transparent process and propose a new framework, through notice-and-comment rulemaking, that identifies gaps in oversight and how agencies could fill those gaps while avoiding contradictory and ambiguous regulations. In those areas where CLIA regulations may overlap with other regulations, such as for analytic validation, inspections and quality systems, we strongly recommend deference to the CLIA requirements. CLIA has been the primary federal law

governing labs, and its flexibility has allowed labs to innovate, making tremendous recent progress in the identification and treatment of diseases.

NOTICE-AND-COMMENT RULEMAKING NEEDED IF FDA INTENDS TO REGULATE LDTS

If the FDA nevertheless intends to proceed to regulate hospital and other laboratories that provide LDT testing services as device manufacturers, as the draft guidance demonstrates, we urge the agency to withdraw the draft guidance and instead issue proposed new requirements through notice-and-comment rulemaking. The AHA reaffirms the recommendations made in a Nov. 18, 2014 letter to the FDA, which was signed by the AHA, American Medical Association, American Clinical Laboratory Association and 48 other organizations. In the letter, we stated that the FDA draft guidance documents conflict with existing regulations specifically exempting clinical laboratories from direct FDA regulation. We also stated that, although the guidance would impose new substantial requirements on clinical laboratories, hospitals, physicians and other health care providers, it does not comply with notice-and-comment rulemaking, as the Administrative Procedures Act (APA) would require.

The law requires notice-and-comment rulemaking in situations, like the current one, where the agency seeks to impose new, significant regulatory obligations on the field. Notice-and-comment rulemaking would ensure that hospitals and other affected parties are afforded the important protections mandated by law. These include having clear and specific notice of all issues a rulemaking is intended to address and, thereby, facilitate the submission of informed and thoughtful comment to the FDA. In addition, affected parties would be assured they receive a precise explanation from the agency about how it considered the comments received and reconciled competing interests, sufficient to justify the agency's final policy choices. In this case, that explanation would presumably include reconciliation of the apparent conflict with the agency's existing regulation that exempts clinical laboratories from direct FDA regulation. Notice-and-comment rulemaking also would require that the FDA evaluate the economic impact of new regulatory requirements and oversight on the regulated parties by providing an analysis of estimated regulatory burdens and costs imposed. **While the AHA provides comments below on the content of the FDA's draft guidance, this should not be interpreted as an abandonment or relinquishment of our view that notice-and-comment rulemaking is required before the FDA can make sweeping and wholesale substantive changes, like those described in the current guidance documents, to the way in which clinical laboratories services are regulated.**

IF FDA INTENDS TO FINALIZE ITS GUIDANCE, CHANGES MUST BE MADE

Modifications to FDA-approved Tests. Hospital laboratories often purchase FDA-approved test kits and modify them, thereby creating LDTs. This improves the performance of the diagnostics, addresses problems or issues with the FDA-cleared or FDA-approved devices, and allows the latest research and clinical knowledge to be rapidly incorporated. These LDTs are regulated by CLIA and must undergo validation prior to their use for patients. Minor changes include such things as modifying scoring systems or adding specimen types that are dictated by medical guidelines or regulations (e.g., National Comprehensive Cancer Network, American Society of Clinical Oncology or CAP). These changes are intended to improve testing accuracy and safety.

However, in the draft guidance, FDA states that "a clinical laboratory that modifies an FDA cleared/ approved device in a way that affects device performance or intended use is considered to be a device remanufacturer… These modified devices must meet pre-market submission requirements." **To require a laboratory to undergo such a burdensome and expensive pre-market review process in order to make modifications to an FDA-approved test kit is unreasonable and violates the prohibition on the FDA regulating the practice of medicine.** This onerous requirement will be a disincentive for laboratories that otherwise would make such changes to improve the capabilities of FDA-approved tests. This will harm patient access to the most advanced diagnostics. **The AHA believes that only clinically meaningful and high-risk performance modifications to commercial kits should be required to meet pre-market requirements.**

Proposals to Exempt Certain LDTs from FDA Enforcement are Insufficient. Under the draft guidelines, the FDA states its intent to continue to use "enforcement discretion," that is, to use its discretionary authority to not enforce the applicable pre-market review requirements and quality systems requirements (but to enforce other applicable regulatory requirements, including notification and adverse event reporting) for several categories of LDTs including: low-risk LDTs, LDTs for rare diseases, traditional LDTs and LDTs for unmet needs. **While the AHA supports these exemptions, broadly speaking, and appreciates the FDA's efforts to identify situations that it believes merit continued enforcement discretion, we find the FDA's draft exemptions to be far too narrowly drawn and unworkable. The AHA has concerns and recommendations for each of these categories.**

Low-risk LDTs (Class I Devices). In general, the AHA supports the use of enforcement discretion for those LDTs the FDA determines to be low-risk. Indeed, rather than partial enforcement discretion, we recommend that these LDTs be safely placed under full FDA enforcement discretion by virtue of their low risk and the fact that, under CLIA, all LDTs are considered high-complexity tests, subject to the most stringent level of requirements. Laboratories producing these LDTs also are subject to state regulatory oversight and many seek accreditation from CAP or other accreditation bodies. **Therefore, it is our view that the labs that offer low-risk LDTs should not only be exempted from pre-market review and quality systems requirements, but also exempted from all FDA regulation, including notification and manufacturer adverse event reporting.** These labs already report adverse events as user facilities and are subject to proficiency testing and inspection under CLIA.

LDTs for Rare Diseases. **The AHA believes that it is appropriate to provide an exemption from enforcement for LDTs for rare diseases because LDTs are often the only option for those with suspected rare diseases.** The commercial market for these tests is largely absent, making continued access to LDTs essential for physicians and their patients.

However, the FDA's draft definition of what would qualify for this rare diseases exemption is insufficient. In the draft framework, the FDA states that "[a]n IVD device may qualify for Humanitarian Use Device designation when the number of persons who may be tested with the device is fewer than 4,000 per year." This threshold is far too low to ensure the continued availability of LDTs for rare diseases. Further, it describes rarely performed tests, not rare diseases. For instance, all newborns undergo screening tests for a range of rare and dangerous

conditions. Many infants (far more than the 4,000 test threshold recommended by the FDA) need to be tested in order to identify the very few who are afflicted with these rare diseases. However, under the FDA's draft definition, none of these newborn screening tests would qualify for enforcement discretion as rare diseases. These tests, therefore, would be subject to burdensome FDA regulation that would likely mean hospitals would no longer be able to offer them to physician and patients. **The FDA, in coordination with appropriate experts, should re-evaluate the draft definition for rare disease LDTs in order to determine an appropriate threshold, which should be tied to the incidence of the disease rather than the volume of tests performed.**

Traditional LDTs. **The AHA recommends that traditional LDTs continue to be exempted from all FDA regulatory enforcement, including from notification and adverse event reporting.** For the same reasons noted above for low-risk LDTs, traditional LDTs are subject to oversight from CLIA high-complexity testing requirements, state regulation and laboratory accreditation. This provides assurance of high-quality, validated testing, obviating the need for overlapping and redundant FDA regulation.

Further, we do not agree that the definition of a traditional LDT should be limited, as the FDA proposes, only to those LDTs that are produced and used by a health care facility laboratory for patients that are diagnosed and/or treated at that same health care facility or within the facility's health care system. **We recommend that the definition of a traditional LDT be broadened to also encompass testing of samples from individuals who are not patients of the health care system.** Many hospitals, particularly large hospitals and academic medical centers, have for many years offered testing services, not only to their own patients but also via "outreach testing" services, to patients of their local community providers. With outreach testing, patient samples from community providers are sent to the hospital's laboratory for testing and the results are communicated by the laboratory physician back to the ordering physician. Among other benefits, outreach testing provides access to testing services and allows patients to continue to seek convenient treatment in their own community. Given increasingly sophisticated communication tools and the ability to rapidly and accurately exchange information regarding testing services, consultation between laboratory physicians and treating physicians can easily occur anywhere. Thus, monitoring of laboratory services and meaningful consultation with treating physicians can, and does take place even when the patients are at a distance.

However, the prospect of having to come into compliance with costly and burdensome FDA device regulations would likely result in many hospital laboratories no longer offering outreach testing to local community providers. **Unless the FDA broadens the definition of traditional LDT to encompass the testing of non-patient samples, the ability of many providers, especially those in rural areas, to continue to diagnose and treat vulnerable populations in their community will be endangered.**

LDTs for Unmet Needs. The AHA appreciates the FDA's recognition of the important role that LDTs play in meeting urgent, but otherwise unmet health care needs. Similar to tests for rare diseases, many LDTs for unmet needs are developed by hospital labs because FDA-cleared commercial kits do not exist for these intended uses. In fact, the term "LDTs for unmet needs" is misleading because hospital laboratories that provide these testing services are actively meeting

patient needs. The agency proposes to temporarily maintain the availability of LDTs that serve unmet needs by exercising enforcement discretion for pre-market review and quality systems requirements for these testing services until a comparable FDA-approved or FDA-cleared kit for the same intended use becomes available. The FDA would consider several factors in determining whether a test is an LDT for unmet needs, including whether there is no other FDA-approved or FDA-cleared kit available for that intended use, and, similar to "traditional LDTs," whether the LDT is both manufactured and used by a health care facility laboratory for a patient who is being diagnosed and/or treated at that same health care facility or within the facility's health care system.

The AHA recommends that the FDA consider a policy that would allow the unmet needs exemption to remain in place until at least a few commercial kits are cleared. By definition, LDTs for unmet needs constitute the standard of care. The hospitals and clinics that offer them continually improve upon these services as new research data becomes available. In addition, this investment in test development and innovation over many years has positioned these labs to respond quickly in emergent situations, such as the H1N1 epidemic and the anthrax cases, by rapidly developing and validating LDTs for emerging infections and making them available to providers nationwide. This ability to rapidly "turn on a dime" to develop LDTs would not be possible under a cumbersome FDA regulatory structure.

Yet, the FDA's draft exemption for an unmet needs test category ends as soon as the FDA approves or clears a single commercial kit for a comparable intended use. When this happens, every laboratory that has developed a comparable LDT testing protocol would need to submit it to the FDA in order to meet pre-market requirements and eventually comply with all of the other FDA device requirements. Many labs likely would find the expense and burden required for such an activity infeasible, leading them to discontinue this testing. This would freeze further innovation and improvements to testing, leaving patients without access to cutting-edge care.

In addition, for all the reasons described above, the AHA remains opposed to the draft requirement that an LDT for an unmet need would receive an exemption from regulation only if the test was developed and used for patients treated in the same health care facility or health system. Some of the nation's most well-regarded health care systems, such as Mayo Clinic, have reference labs that offer a wide range of LDTs to physicians and other providers nationwide, including tests developed for unmet needs. Such reference labs benefit patients by extending access to LDTs for unmet needs, as well as other testing services, far beyond the health care facility in which these laboratory services are developed and run.

Thank you again for the opportunity to comment. If you have any questions, please contact me or Roslyne Schulman, director for policy development, at (202) 626-2273 or rschulman@aha.org.

Sincerely,

/s/

Rick Pollack
Executive Vice President