



February 2, 2015

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

Re: Framework for Regulatory Oversight of Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; [Docket No. FDA-2011-D-0360]

Dear Commissioner Hamburg:

The American Association of Bioanalysts (AAB) and the National Independent Laboratory Association (NILA) welcome the opportunity to provide comments on the Food and Drug Administration's (FDA) proposed Framework for Regulatory Oversight of Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories. AAB is a national professional association whose members include clinical laboratory directors, owners, managers, medical technologists, and physician office laboratory technicians. NILA's members are community-based laboratories that range in size from intra-state to multi-state regional laboratories.

Since 1949, AAB has administered one of the nation's full-service proficiency testing programs approved by the Clinical Laboratory Improvement Amendments of 1988 (CLIA), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Centers for Medicaid and Medicare Service (CMS), and all state agencies to satisfy laboratory proficiency testing requirements.

Position of AAB and NILA on Regulation of LDTs

AAB and NILA believe that when the clinical laboratory stakeholder community deliberates on the oversight of laboratory developed tests, both patient safety and advancing access to innovative tests must be paramount. The purpose of these tests is to offer patients the potential to prevent disease, obtain early diagnoses, and receive the most accurate and best course of treatment from their health care providers. Physicians and patients must be able to rely on and trust the results provided from an LDT.

As health care providers and as providers of federal- and state-approved proficiency testing, AAB strongly believes a thorough and non-burdensome process must be in place to ensure that LDT technology is accurate, reliable and reproducible, and that such a process can be achieved. The primary purpose of regulatory oversight should be to avoid potentially life-altering or life-threatening implications from an inaccurate or misleading test result.

AAB and NILA agree with the FDA's assertion that the number and complexity of LDTs has increased in recent years. However, advancement in LDTs does not merit an overhaul of the regulatory process to oversee these tests. AAB and NILA disagree with FDA's opinion that there is no current process in place to oversee LDTs and believe that for an appropriate regulatory structure to be developed, the FDA must first recognize the structure that already exists, both through CLIA and state government agencies, in addition to private sector accreditation programs. Our organizations believe we need to modernize current programs that exist to ensure they appropriately oversee the number and type of LDTs being offered today and that we likewise consider where new oversight may be needed when gaps exist. We must work collaboratively to ensure that any new regulatory processes do not result in barriers toward laboratories developing LDTs to meet clinical needs, support vulnerable patient populations, or address public health emergencies.

AAB and NILA support the FDA's guidance proposal to establish a risk-based classification approach toward developing the level of federal oversight needed for different types of LDTs. We support the categories as outlined in the guidance: high, moderate, and low risk. We believe that the CMS and FDA should jointly oversee specific types of LDTs deemed through a public stakeholder review and engagement to be high risk LDTs. We believe that a separate regulatory pathway for high risk tests must be established within the FDA that recognizes LDTs as services not as medical devices. For other tests, we believe the regulation of LDTs should remain under the jurisdiction of CLIA.

AAB and NILA's position on the regulation of LDTs and comments on the proposed guidances focus on the following tenants:

- Any new regulation of LDTs must be done through notice and comment rulemaking and an economic impact analysis must be conducted.
- LDTs should not be regulated as medical devices and should be regulated through a different regulatory pathway than that for medical devices.
- The oversight of LDTs should be through a risk-based approach that ensures both the analytic and clinical validity of all LDTs.
- CLIA can and should be modernized to support the oversight of most LDTs.

Regulatory Oversight of LDTs

AAB and NILA strongly believe that any proposed new regulatory oversight for laboratory developed testing must be issued by the overseeing agency(ies) through notice and comment rulemaking as required under the Administrative Procedures Act (APA). Our organizations believe that as outlined, the FDA guidances would constitute a substantive rule, and therefore, the FDA has a legal obligation to proceed through notice and comment rulemaking. Through its guidance documents, the FDA has outlined a new regulatory regime for LDTs with many terms lacking specificity. Yet, the guidances go further than interpreting current FDA rules or policy and instead impose binding legal obligations that have never before applied to clinical laboratories. AAB and NILA believe laboratories have a legal right to have the agency formally respond to questions and concerns raised through a formal regulatory comment period.

A formal regulation also ensures that the agency conducts an economic impact analysis of the new regulatory oversight process to assess the burden on the industry it seeks to regulate and the costs associated with a dual jurisdiction over clinical laboratories through the FDA and CMS. AAB and NILA believe such an economic analysis is critically important. Our organizations are particularly concerned about the economic burden a new regulatory regime, such as the one proposed in the draft guidance, would have on community/regional clinical laboratories that conduct LDTs, affecting their ability to continue to invest in this testing market and compete with large national laboratory providers who have vastly more resources to support the costs associated with any new regulatory oversight process.

Regulatory Authority – Medical Devices

AAB and NILA believe that laboratory developed tests are distinctly different than medical devices. LDTs are services directed by Ph.D. laboratory scientists and physicians to meet specific patient needs in reference to their clinical condition. LDTs are performed at the request of a physician, and the laboratory provides no physical product. Rather, the laboratory provides information and data for physicians to utilize in making clinical decisions. Laboratories offer a methodology based on their analysis to provide information to the treating provider – they do not provide commercial products. LDTs are not packaged and shipped in interstate commerce. LDTs are not sold as test kits for others to use – there is no physical product.

The Federal Food Drug and Cosmetic Act (FDCA) recognizes a distinction between devices and laboratory tests. Devices are defined as articles of commerce, not as services. The FDCA does provide the FDA authority over clinical test kits as well as in vitro reagents, but LDTs are neither a test kit nor a reagent. In recognizing distinctions between devices and testing services, Congress created a separate regulatory regime for laboratory tests under the Centers for Medicare and Medicaid Services (CMS) through the establishment of CLIA.

As a result, AAB and NILA do not support having LDTs fall under the FDA’s regulatory authority as medical devices nor do we support having the current FDA medical device safety and effectiveness requirements apply to laboratory testing services. Manufactured articles of commerce (e.g., drugs and medical devices) raise significantly different regulatory issues and concerns from LDTs. Manufacturer test kits, for example, are sent to any provider that requests them, and once sent, the manufacturers have no control over a kit’s performance nor the conditions it is subjected to that may affect its performance (e.g., altitude, temperature control). In contrast, LDTs are only performed in a single laboratory, and the result, not the test itself is sent out. The laboratory has complete control over the performance of the test. Manufacturer test kits are used by a variety of personnel, and training on use is unknown. LDTs are overseen by the laboratory director and used by controlled and trained personnel. The oversight needs differ greatly between test kits and LDTs. The issues of concern raised on such matters as determining the clinical validity of LDTs, outlining a risk protocol for laboratory tests, and ensuring appropriate pre-and post-market oversight merit much further deliberation and a process that falls outside of the traditional FDA medical device oversight process.

While the landscape of laboratory testing may have evolved significantly from when CLIA was amended in 1988, this does not mean that the statutory structure in place must be completely altered. What it does mean is that CLIA very well should be modernized to meet changes in current laboratory testing services. And, the FDA should focus its attention on those laboratory tests that cannot fit within a modernized CLIA structure. Rather than attempt to fit a square peg in a round hole, the FDA should give consideration as to what oversight, evidence and processes are needed to safely and effectively oversee those laboratory tests deemed to be at highest risk and in need of oversight beyond the CLIA process.

Definition of Laboratory Developed Test

The FDA takes an approach of limiting its definition of Laboratory Developed Test to that which is “an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory.” AAB and NILA believe this definition results in some confusion for those clinical laboratories that develop and offer LDTs within their given laboratory network. For these laboratories, the test protocols and methodologies were developed within and with the support of a given lab’s network of laboratories – which is different than a lab transferring a LDT to others in its network. Clarification is needed by the FDA as to whether such a service would be regulated as an LDT under the terms of the guidance document.

The AAB and NILA also question whether and how the FDA plans to oversee a new category of LDTs defined in statute through the *Protecting Access to Medicare Act of 2014* (Public Law 113-93). This new law included a new statutory definition for some LDTs, called “Advanced Diagnostic Tests.” AAB and NILA believe any regulatory process for LDTs must also include these tests so that there is consistency across the market in terms of regulatory review and oversight.

Risk-Based Classification System

AAB and NILA do not agree with or support the regulation of LDTs as medical devices under current statute. As explained above, we believe that the risks posed by clinical laboratory developed tests are different from those posed by medical devices, including FDA-approved commercial test kits. However, AAB and NILA do support the regulation of these tests through a risk-based classification system that involves both the FDA and CMS and ensures the analytic and clinical validity for all LDTs.

AAB and NILA are alarmed, however, that in the absence of producing any formal risk classification criteria, the FDA has sought to outline a timetable for requiring tests it deems high-risk to undergo pre-market agency approval within 12 months after the agency's guidance is finalized. Issuing a formal framework without providing any guidance on risk classification criteria is inappropriate and leaves clinical laboratories uncertain as to how the tests they provide would be classified and whether they will be required to meet FDA requirements within a short period of time after the guidance is finalized.

AAB and NILA do not believe the FDA should have sole authority to determine where a given LDT falls within a risk classification system. Any new risk-classification review system for clinical laboratory testing must involve stakeholders to ensure a process that fairly assesses the risk of a given test and the evidence needed to demonstrate the test's analytical and clinical validity. Stakeholder input must be through a formal process that includes a panel assessment or advisory committee with the panel/committee including a broad representation of FDA officials, CMS-CLIA officials, clinical laboratories (including specialized testing labs, community laboratory providers, and national laboratory providers), physicians, patient representatives, and organizations with experience and expertise in proficiency testing and accreditation processes. Stakeholder feedback must be instrumental in final decision making around risk classification for tests. The process for determining risk classification for categories of tests should also involve a formal notice and comment rulemaking where categories of testing are being recommended as high-risk.

The FDA must also consider that under CLIA there are currently processes in place to assess low, moderate, and high complexity testing. These processes include CLIA certification, assessing a lab's performance and test accuracy and reliability; ongoing proficiency testing; and frequently, accreditation by a third-party organization. Rather than dismiss those processes, the FDA should reflect on those processes and consider where it is most necessary for any additional oversight protections. It is the position of AAB and NILA that for most laboratory developed tests, these current processes, once enhanced with necessary modernizations to CLIA, can best be overseen through CLIA.

AAB and NILA are mostly concerned with the testing conducted by laboratories that utilize complex, non-transparent, proprietary algorithms to predict risk of, progression of, or patient

eligibility for a specific therapy to respond to and/or treat a disease. We believe that these tests impose the highest risk to a patient's health and well being given the risk of serious morbidity or mortality. Our concern is that these types of tests cannot be evaluated using traditional processes or traditional processes with simple modifications. Specifically, there can be no inter-laboratory comparisons performed to validate the test results. Having the FDA focus its review efforts on this category of testing would be appropriate to ensure the analytical and clinical validity of these highly specialized tests.

Regardless of which agency ultimately has primary jurisdiction over a given classification of tests, it is important that any new regulatory system not be so burdensome that it eliminates innovation in laboratory testing. There should be a phase-in for current tests on the market, and such a phase-in would be required if a new advisory committee is to be established to support FDA-CMS/CLIA efforts to define test risk levels. The AAB and NILA do not believe that all current diagnostic tests should be grandfathered into the marketplace. All tests need to be assessed for analytical and clinical validity, and this will need to be done over an extended timetable, which could be as long as three-to-five years, given the volume of tests currently on the market.

Pre-Market Oversight

Because LDTs are a service and not a commercial entity, pre-market oversight under the traditional device pre-market process is inappropriate and the outline offered in the guidance document for pre-market review should not be the process undertaken to ensure the safety and efficacy of an LDT before it is utilized by health care providers with patients. A regulatory pathway that recognizes the LDT to be a pre-clinical service and seeks to assess the test's validity is the appropriate process for overseeing these tests. AAB and NILA advise the FDA to reconsider the approach outlined in the guidance for pre-market review and consider use of standards developed by the Clinical Laboratory Standards Institute (CLSI), including consensus standards CLSI developed with the FDA, to support the review of pre-clinical testing services offered by laboratories.

Post-Market Oversight

Post-market assessment is paramount to ensuring the safety and efficacy of LDTs available to patients. External quality control programs that currently exist through the CLIA-based proficiency testing program tell the agency how well traditional laboratory tests are performing in the field. Over the years, this process has not resulted in barriers to patient access to laboratory tests. However, the current proficiency testing program must be modified in order to adequately assess LDTs, since LDTs are, by definition, only being conducted by a single laboratory and test result samples from that laboratory cannot be tested in comparison to samples from other laboratories. A modified proficiency testing program is needed to ensure

that the testing results from a single lab can be replicated and shown to be accurate and reproducible.

AAB has begun a review of how a modified PT program could be structured to assess the validity of LDT test samples, and we encourage an open dialogue between the FDA, CMS and PT providers to establish such a program. We envision a system where laboratories can provide LDT samples to a PT provider, and the PT provider will serve as an honest broker, de-identifying the sample and providing it as an unknown to a laboratory. In rare instances, it may not be possible for a sample to leave a laboratory testing facility, in which case the justification would need to be agreed to by the PT provider. The laboratory would be required to have a person different than the testing personnel de-identify the samples. This person would also be responsible for submitting the answer key and results to the PT provider for grading. In such cases, a signed attestation by the sample preparer and the testing personnel should be included with the results indicating that the intended results were not provided to the testing personnel in advance and that the results have not been altered after initial testing. Where possible, sufficient proof of the results obtained (instrument output, etc.) should be kept with the PT testing records to support that the reported results were in fact obtained during testing. Samples could be derived from a variety of sources: tissue obtained from laboratory, cell culture, microbiological sample, genetically altered organisms or synthetic constructs. A modified PT program for LDTs would be designed cooperatively by the laboratory and the PT provider. The PT provider would ensure that the program meets basic PT guidelines, and the laboratory would be responsible for designing a program that best assesses the accuracy of their method. Minimum criteria for a modified LDT PT program would be:

- Assessments conducted two or three times a year with a minimum of six samples.
- Where possible, the program should be designed to compare results from multiple sites or laboratories. If no definitive gold standard sample or method is available, the results would be compared to peer group consensus (consensus being defined as 80% agreement among all laboratories reporting).
- When only a single laboratory performs a test, the correct answer may be defined as the testing laboratory being able to repeatedly achieve the same results through time. The original accuracy being defined through clinical correlation and accuracy, in this case, being defined as being able to reproduce the results obtained.
- Samples should cover all reportable results produced by the test.
- Samples should cover all clinically significant levels or qualitative results produced by the test.
- Samples should, where possible, cover all aspects critical to the test (pre-analytical, analytical, post-analytical). It is understood that some sample types such as surgical biopsies will likely require an analog sample, which will not fully cover all pre-analytical aspects.

- Samples should strike an efficacious balance between accurately reflecting an actual test sample and meeting needed stability, reproducibility, and cost requirements.
- Grading of the results would be the responsibility of the PT provider. Results would be presented to the laboratory in a clear and timely fashion.
- Misses and failures in an LDT PT event would require the same follow up and potentially corrective action as any traditional PT event.
- If the root cause of a failure is determined to be in the design of the LDT PT, it would be the responsibility of the laboratory to bring this to the PT provider's attention and to work with the PT provider to improve the PT design. It is the responsibility of the PT provider to ensure the root cause attributing failure to the PT design is reasonable and that any new PT design meets the overall PT requirements.
- The laboratory would be responsible for paying all costs associated with the PT program, including, but not limited to; sample costs, shipping, storage and reasonable overhead costs incurred by the PT provider (personnel, space, miscellaneous office and business expenses).
- Unless there is an overriding technical reason where the PT provider cannot provide acceptable specimens for PT, PT providers cannot be changed during the calendar year. The laboratory would be free to switch providers at the end of any calendar year.

LDT PT would be, in all other ways, identical to the requirements as set forth in CLIA or other authoritative quality documents to which the laboratory is subject; e.g., individual states, JCAHO, CAP.

In addition, current CLIA requirements for proficiency testing for specific specialties and subspecialties (e.g., virology, chemistry, endocrinology) must be broadened to cover all categories of laboratory testing not currently included in CLIA's list of covered analytes (e.g., genetic testing).

Regulatory Overlap – FFDCa and CLIA

Both the FDA and CLIA share the same regulatory goal of ensuring correct laboratory test results, and as such, there is much overlap in what is being proposed within the FDA guidance and the current CLIA regulatory process. While the FDA is seeking to address the safety, effectiveness, and development of the tests, CLIA is currently regulating the quality of the clinical testing process, the quality of the laboratory performing the testing, and assessing the performance of the tests "in the field."

The FDA has not issued any information as part of its proposed guidance on how Quality Systems Regulation (QSR) applicable to devices under the FDA would interact with quality requirements under CLIA. CLIA already has an extensive quality control process that involves proficiency testing, internal quality controls, and external quality controls. The FDA has

demonstrated that regardless of current QSRs, it does not even have external quality controls in place for how waived tests approved by the agency perform in the field. There have been numerous documented problems for tests approved by the FDA as waived, with little-to-no quality assessment. With the inability to even appropriately assess the tests it categorizes as waived, AAB and NILA have serious concerns about how the agency can and will appropriately assess the quality of LDTs.

Regulatory Oversight of Tests for Rare Diseases, Unmet Needs, Emergency Purposes

LDTs have resulted in promise for patients facing rare/orphan diseases, particularly where IVD manufacturers do not find it profitable to work toward development of a product for a limited population. Any new regulatory process for LDTs must not be so burdensome as to eliminate innovations for these vulnerable patient groups. The AAB and NILA recommend excluding LDTs for rare/orphan diseases from any regulatory process until the tests meet a high-volume threshold and are commonly used in the general market, where risk to public health could be substantially increased.

Likewise, any regulatory system for LDTs must not impose lengthy burdensome requirements on tests used for emergency purposes (e.g., Ebola). Where the public health is more greatly served by the availability of testing to support early diagnosis and treatment options during emergencies, the government must maintain an emergency system that allows for such flexibility and does not squander innovation. AAB and NILA recommend excluding LDTs for emergency purposes (e.g., public health concerns) from any new regulatory process until the tests may meet a high-volume threshold and are commonly used in the general market, where risk to public health could be substantially increased.

Conclusion

AAB and NILA thank the FDA for the opportunity to provide comments on the agency's guidance document. Our organizations are committed to working with the FDA, CMS, the patient community, and others to address the issues raised in the FDA's proposed guidance documents. It is important that we collaborate to ensure that a fair and sustainable regulatory process is in place to assess the quality and safety of LDTs while allowing for continued innovation to support patient testing needs.

The deliberations over the oversight of LDTs show that careful consideration must be made over a multitude of issues. To assume these tests appropriately fit into the FDA's current regulatory oversight and clearance process for medical devices is flawed thinking. Our organizations respectfully request that the agency withdraw the guidances as outlined and work with the stakeholder community, Congress, and CMS to establish an appropriate process and infrastructure that first recognizes LDTs as different from medical devices and also recognizes that existing government oversight processes at the federal and state level can help

streamline the focus for any new regulatory oversight process, allowing the FDA to focus on those tests ultimately classified as high risk. Thank you for the opportunity to provide feedback on the guidance. Should you have any questions, or require additional information, please contact Julie Scott Allen, our Washington representative, at (202) 230-5126 or julie.allen@dbr.com.

Sincerely yours,

A handwritten signature in blue ink that reads "Mark S. Birenbaum". The signature is fluid and cursive, with a long horizontal flourish at the end.

Mark S. Birenbaum, Ph.D.
Administrator