



February 23, 2015

The Honorable Lamar Alexander
Chairman
Senate Committee on Health, Labor, Education and Pensions
428 Senate Dirksen Office Building
Washington, DC 20510

The Honorable Richard Burr
217 Russell Senate Office Building
Washington, DC 20510

RE: Comments in Response to the Report: Innovation for Healthier Americans- Identifying Opportunities for Meaningful Reform to Our Nation's Medical Product Discovery and Development; Submitted Electronically via Innovations@help.senate.gov

Dear Chairman Alexander and Senator Burr:

On behalf of the American Association of Bioanalysts (AAB) and National Independent Laboratory Association (NILA), I am pleased to provide comments in response to the Committee's recently released report, *Innovation for Healthier Americans: Identifying Opportunities for Meaningful Reform to Our Nation's Medical Product Discovery and Development*. 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 intrastate to multi-state regional laboratories.

Since 1949, AAB has administered one of the nation's largest, 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.

AAB and NILA are pleased to specifically respond to Sections IV and VII of the Committee's report, to address the important issues related to regulation and oversight of laboratory developed tests (LDTs).

Background

Position of AAB and NILA on the Regulation of LDTs

AAB and NILA believe that when the clinical laboratory stakeholder community deliberates on the oversight of laboratory developed tests (LDTs), 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 assertion in the FDA's proposed *Framework for Regulatory Oversight of Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories* (October 2014) that the number and complexity of LDTs has increased in recent years. However, our organizations do not believe that the advancement in LDTs merits an overhaul of the regulatory process to oversee these tests. AAB and NILA disagree with the 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 establishment of a risk-based classification approach toward developing the level of federal oversight needed for different types of LDTs, classifying tests as 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 diagnostic tests must be established within the FDA that recognizes LDTs as services not as medical devices. For other tests, we believe the regulation and oversight of LDTs should remain under the jurisdiction of CLIA.

As the Committee deliberates on issues related to the oversight of LDT's, AAB and NILA strongly advise the Committee to consider the following position:

- 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 and involves a formal stakeholder process.
- CLIA can and should be modernized to support the oversight of most LDTs.

Response to Committee Report Questions

Section IV: How do we ensure that appropriate congressional oversight of NIH and FDA produce better metrics on the federal government's efforts to advance new medical products, including oversight of the medical product development pathways for drugs, devices, and diagnostics?

FDA regulatory processes must fairly assess the quality and safety of diagnostics, including LDTs, but must not be so burdensome and economically challenging as to squander investment in the growth of such diagnostics. Congress must ensure that any regulatory process does not prohibit new diagnostics from coming to market, and as a result, restrict patient access to needed diagnostic testing services.

Congress specifically set up a distinct statutory process for the oversight of laboratory tests through CLIA, not through the Federal Food Drug and Cosmetic Act (FDCA). Congress should seek to understand CLIA's role in the oversight of laboratory testing and where the program can be modernized to ensure it is keeping paces with changes in laboratory practice to appropriately oversee the safety, reliability, and reproducibility of laboratory tests, including LDTs.

Congress through legislative history and in establishing the Federal Food Drug and Cosmetic Act (FDCA) defined devices as articles that are sold in interstate commerce, providing oversight for such devices to be under the jurisdiction of the FDA. Congress needs to question whether other medical innovations, including LDTs fit within this authority. LDTs are not sold in interstate commerce, and therefore, do not meet the definition of device under existing statute. Congress should ensure that no federal agency inappropriately classifies LDTs in order to establish or justify a new regulatory process for oversight.

Section VII: Should there be a larger public debate on the FDA's use of guidances rather than rulemaking to communicate FDA policy? What are the implications of current practices for patients, doctors, industry, and scientists?

AAB and NILA recommend that there be a larger deliberation on the FDA's use of guidances over notice and comment rulemaking. When requirements being issued by the FDA seek to impose new regulatory processes with significant penalties for non-compliance and significant economic consequences on industry in order to comply, then industry must have the protections and process supported through notice and comment rulemaking.

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 proposed guidances on LDTs issued in October 2014 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 all 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 FDA's 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.

Section VII: Given the advances in medical products, is it time to reassess whether separate centers are the right way to regulate medical products? Are there other ways of organizing the agency and regulatory pathways – based on disease areas, for example– that may be more efficient and effective?

AAB and NILA believe that Congress must ensure that the FDA recognizes the distinction and uniqueness of medical products – drugs and devices to those of pre-clinical services, such as LDTs and seeks to oversee these different technologies in a manner that recognizes their differences and can appropriately ensure the safety and efficacy of each. We do believe it is time to reassess whether separate centers are needed to support separate regulatory pathways in an effort not to treat technologies the same and “fit a square peg in a round hole.” This assessment should seek to understand where new regulatory pathways need to be set up within a specific agency, including the FDA and also consider where there should be dual-agency regulatory structures to appropriately oversee technology and to do so in a way that ensures appropriate use of federal resources and expertise without establishing a duplicative regulatory process.

A significant example of where there is a need for a separate center and/or regulatory pathway is in regard to the oversight of LDTs. LDTs differ significantly from FDA-regulated medical devices in that LDTs are services directed by Ph.D. laboratory scientists and physicians to meet specific patient needs – not device products or articles. They are proprietary professional interpretive services made available to treating medical professionals at their request, not physical products. The services included through LDTs include the design, development, and validation of a test, and the interpretation of LDT results. LDTs are not packaged and shipped in interstate commerce or sold as test kits for others to use. Because LDTs are pre-clinical services and not devices, they deem a separate regulatory pathway.

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.

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. 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.

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.

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. 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.

Section VII: How can Congress help ensure the FDA is appropriately organized to enable the agency to more efficiently review medical products and perform post-market surveillance?

To appropriately answer these questions, Congress must look at each medical product and medical service individually on its own merits and consider what post-market surveillance process is already in place to oversee each individual product and service. In regard to LDTs, given that these are pre-clinical services not products, they deem a different regulatory pathway than devices or drugs.

AAB and NILA support the regulation of LDTs through a risk-based classification approach that ensures the analytic and clinical validity for all LDTs. Our organizations believe that regulatory oversight should be under the FDA or CMS/CLIA, depending on the level of risk classification: high risk (FDA oversight); moderate risk (CMS/CLIA oversight); low risk (CMS/CLIA oversight). There is precedent for such an approach under FDA and CLIA, as CLIA certification for laboratories is based on the level of complexity of testing that a laboratory performs: waived (low); moderate; high complexity.

AAB and NILA also believe that because of the many challenges the federal agencies have currently had in defining risk in relation to LDTs, a formal process must be established to ensure stakeholder feedback is received and can be acted on. AAB and NILA urge Congress to establish a federal advisory committee and require a notice and comment rulemaking process to provide insight into the risk classification process and allow for interagency and outside expertise, including the FDA, CMS/CLIA, federal agencies, and professional organizations that represent clinical laboratories, physicians, consumers, and organizations with experience and expertise in proficiency testing and accreditation processes. CLIA must also be modernized, including improvement to its oversight structure, ability to assess clinical validity, and the need to modify proficiency testing programs to address changes in the complexity of laboratory testing and where testing is proprietary and cannot currently be assessed using traditional proficiency testing processes.

The risk level for each test should be determined based on the potential for a misinterpreted test result to cause harm (death or disability) to a patient or have a significant adverse effect on public health. The risk assessment process must also consider the transparency of the test methodology utilized, including whether the laboratory utilizes complex and proprietary algorithms or software to establish a test result that could result in increased risk to a patient.

Post-market assessment is paramount to ensuring the safety and efficacy of LDTs available to patients, but Congress must consider that post-market review for LDTs is best suited for the agency with expertise

in conducting such assessments – CLIA, and not the FDA. External quality control programs currently exist through the CLIA-based proficiency testing program and tell the agency how well traditional laboratory tests are performing out in the field, and over the years, this process has proven to not result 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 the lab cannot be tested in comparison to samples from other laboratories. A modified proficiency testing program would need to ensure that the testing results from a single lab can be replicated and shown to be safe, effective, and reproducible. AAB has begun a review of how a modified PT program could be structured to assess the validity of LDT samples, and we encourage an open dialogue between Congress, FDA, CMS and PT providers to ensure the establishment of such a program. Additionally, current CLIA requirements for proficiency testing for specific specialties and subspecialties (e.g., virology, chemistry, and endocrinology) must be broadened to cover all categories of testing.

Section VII: How should the FDA rely on outside science when developing policy? How should FDA then communicate timely scientific and regulatory policy changes while still allowing for public comment and debate?

A leading example of where it is critically important for the FDA to seek outside scientific expertise when developing policy is the oversight of LDTs. AAB and NILA are extremely alarmed that in the absence of working with stakeholders or conducting any deliberate process or criteria, the FDA has sought (via its proposed rule) to outline a timetable for requiring laboratory developed tests the agency deems to be high-risk to undergo pre-market agency approval within 12 months after the agency's guidance is finalized. Issuing a formal regulatory 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 believe that this illustrates exactly why outside stakeholder support is needed. Our organizations 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 outside 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.

Conclusion

Thank you again for the opportunity to provide a response on these important issues. AAB and NILA are committed to working with the Committee to ensure that a fair and sustainable process is in place to assess the quality and safety of LDTs while allowing for continued innovation to support patient testing

needs. We want to work with the Committee to establish an appropriate diagnostic pathway that 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 pathway, allowing the FDA to focus on those tests ultimately classified as high risk. 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 extending to the right.

Mark S. Birenbaum, Ph.D.
Administrator