



January 5, 2015

The Honorable Fred Upton
Chairman
House Energy and Commerce Committee
2183 Rayburn HOB
Washington, DC 20515

The Honorable Diana DeGette
Member
House Energy and Commerce Committee
2368 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Upton and Representative DeGette:

On behalf of the American Association of Bioanalysts (AAB) and National Independent Laboratory Association (NILA), I am pleased to provide a response to the Committee's request for response on the *21st Century Cures Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests*. AAB is a national professional association whose members include clinical laboratory directors, owners, managers, medical technologists, physician office laboratory technicians, and others. NILA's members are community-based laboratories that range in size from intra-state to multi-state regional laboratories. In addition to providing diagnostic laboratory services relied on by physicians across the country every day, a number of AAB and NILA members are engaged in the development of laboratory tests that provide patients and their physicians access to safe and effective testing options.

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.

In response to the Committee's white paper on diagnostic tests and outlined questions, AAB and NILA are pleased to issue the following response:

1. Multiple stakeholders have expressed the urgent need to have clear and logical lines separating the practice of medicine, the actual conduct of a diagnostic test and the development and manufacturing of diagnostic tests. How should these lines be defined and what are the key criteria separating each of these activities?

Clinical laboratory practice and any testing conducted by a laboratory is not the practice of medicine. It does not matter if the clinical laboratory and testing services performed are led by a Ph.D. scientist, pathologist, oncologist, infectious disease specialist, or medical geneticist – clinical laboratory testing is a health care service utilized to support the practice of medicine broadly, and personalized medicine, specifically. A patient's treating physician utilizes testing performed by a laboratory along with a patient examination, review of patient/family medical history, and other factors to support the actual practice of medicine and establish a diagnosis on a patient's condition or decision on how to manage a patient's care. In a situation where a single clinical laboratory develops a new laboratory test, many of these tests are predictive in nature, using complex algorithms to ultimately provide predictive data on a patient's level of risk for a certain disease or condition. Again, these types of tests do not constitute the practice of medicine, as any decision in relation to the test results is the ultimate responsibility of a patient's treating physician.

The Committee must also understand that historically under CLIA and under judicial review, non-medical providers, including Ph.D. scientists are permitted to direct laboratories, including the overall technical and administrative responsibility for the laboratory. The training and expertise of these professionals has been essential at guiding the physician community on test results to support the practice of medicine, but the work of these scientists is not the practice of medicine itself.

Clinical laboratories are not manufacturers but health care providers who offer testing services, not products. These services include consultation with physicians to support the design of new tests, conducting of testing on patient samples, and the interpretation of test results to support physician understanding and decision making. These laboratory activities greatly differ from those of manufacturers who develop and produce in vitro diagnostic test kits, testing instruments, or durable medical equipment that is sold in the open commercial market.

2. In FDA’s draft regulatory framework, the agency describes the extent to which it proposes to regulate LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act (FDCA). It is relatively clear with respect to distributed test kits what constitutes a “device,” but less clear when considering a test developed and performed in a laboratory. What should comprise the “device” subject to regulation by the FDA?

Laboratory developed tests differ significantly from FDA-regulated medical devices in that LDTs are services – not device products or articles. They are proprietary professional interpretive services available to treating medical professionals. The services included through LDTs include the design, development, and validation of a test, and the interpretation of LDT results. Because LDTs are services and not devices, they require a separate regulatory pathway.

LDTs are not described in the Federal Food Drug and Cosmetic Act nor referenced in legislative history as being under the authority of the FDA as regulated devices.

3. FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?

While AAB and NILA does not support the regulation of LDTs as medical devices under current statute, the AAB and NILA does support the regulation of these tests through a risk-based classification approach that ensures the analytic and clinical validity for all LDTs. The AAB and NILA 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 believes 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.

4. The current pre-market review standards that apply to *in vitro* diagnostics use the same terminology of safety and effectiveness that apply to all medical devices. Should the medical device concepts of safety and effectiveness apply to test kits and LDTs?

AAB and NILA do not support the regulation of LDTs as medical devices under current statute, and therefore, does not support the establishment of current pre-market review standards for LDTs or on modifications to an existing FDA-cleared test kit utilized in the development of a LDT.

For those LDTs determined to be high risk upon a process that includes notice and comment rulemaking and a federal advisory committee(per question 3 above), AAB and NILA believe regulatory oversight should be under the jurisdiction of the FDA and that the agency must establish a separate regulatory approval process outside of the current device approval (e.g., PMA) process to assess the analytical and clinical validity, and therefore, the safety and effectiveness of high risk LDTs, including those that modify FDA-cleared test kits.

5. Are there areas where the balance between pre-market reviews versus post-market controls should be reconsidered? How can post-market processes be used to reduce barriers to patient access to new diagnostic tests?

Yes, ensuring both the analytical validity and clinical validity of all LDTs, whether they undergo a pre-market review process by the FDA or CMS/CLIA is essential to ensuring the safety and quality of the test before it is utilized on patients. To do this will require a modernization of existing CLIA processes to require an assessment of clinical validity. To support the pre-market clinical validity review process, AAB and NILA believe the FDA or CLIA must work in tandem with outside accrediting agencies that currently require proof of clinical validity, including the College of American Pathologists (CAP), Joint Commission, and other accrediting organizations.

Post-market assessment is paramount to ensuring the safety and efficacy of LDTs available to patients. 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. 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 (e.g., genetic testing).

6. A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?

As stated in #4 above, AAB and NILA do not support the regulation of LDTs as medical devices under current statute, and therefore, does not support the establishment of current pre-market review standards/submissions for modifications to existing FDA-cleared test kits that are utilized in the development of a LDT. If a FDA-approved test kit is being altered for the purposes of developing a LDT, it is being used for the establishment of a new testing procedure that must be regulated through a separate FDA pathway. If a laboratory is forced to undergo a lengthy and expensive premarket submission process under current FDA requirements, it will hamper development of such LDTs and patient access to such tests.

7. We have heard a lot about the practice of medicine and its relationship with medical product "labeling." What should comprise "labeling" for diagnostic tests? Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices? What about for laboratories that develop, perform, and improve these tests? Should there be regulatory oversight of the information that is provided to the individual patient or health care provider or is that the practice of medicine?

As stated in #1 above, clinical laboratory practice and any testing conducted by a laboratory is not the practice of medicine. Whether laboratory testing services are performed by a Ph.D. scientist, pathologist, oncologist, infectious disease specialist, or medical geneticist – laboratory testing is a health care service utilized to support the practice of medicine broadly, and

personalized medicine, specifically. At a minimum, AAB and NILA believe information should be accessible to patients and health care providers on which federal agency reviewed and approved any given test, the laboratory that performed the test, and how to access publicly available information of the analytic validity of the test results (e.g., proficiency testing results).

8. The Section 1143 guidance documents raise important questions about the relationship between the FDCA and the Clinical Laboratory Improvement Amendments (CLIA), administered by the Centers for Medicare & Medicaid Services (CMS). Is there overlap between the requirements of the guidance documents and CLIA? For instance, how do FDA's quality systems regulations compare with CLIA quality systems requirements? Are there areas of duplication where there would be efficiencies to having either CLIA or FDA regulate, rather than both?

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 and effectiveness of the diagnostic test itself and the quality of the test and manufacture 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 themselves when "out in the field."

The FDA has not issued any information 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 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.

9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g. Ebola)?

LDTs have resulted in promise for patients facing rare/orphan diseases, particularly where IVD manufacturers did 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 such a time 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. The AAB and NILA recommends excluding LDTs for emergency purposes (e.g., public health concerns) from any new regulatory process until such a time 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.

10. Any new regulatory system will create transition challenges. How should existing products be handled? Should all current diagnostic tests be “grandfathered” into the marketplace? What transition process should be used for new product introductions?

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.

The *Protecting Access to Medicare Act of 2014* also included a new statutory definition for some LDTs, called “Advanced Diagnostic Tests.” 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.

11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?

Any regulatory process must fairly assess the analytical and clinical validity of all LDTs, but must not become so burdensome and economically challenging as to squander investment in the growth of LDTs, and as a result, patient access to needed diagnostic testing services.

One incentive would be to establish a regulatory process for moderate and high-risk LDTs that expands upon the 2011 FDA-CMS parallel review process for innovative medical devices, allowing the tests to be considered for coverage and regulatory approval, simultaneously.

AAB and NILA are committed to working with the Committee, the federal agencies, and the patient community to address these challenges. 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.

Conclusion

Thank you again for the opportunity to provide a response on these important issues. AAB and NILA applaud the Committee's focus and work on the 21st Century Cures Initiative. We look forward to continuing to work with you as you address issues related to the regulation of laboratory developed tests. 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