June 19, 2015

The Honorable Fred Upton
Chairman
House Energy and Commerce Committee
2183 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Upton:

On behalf of the American Association of Bioanalysts (AAB) and the National Independent Laboratory Association (NILA), I am pleased to provide comments on the Committee's draft legislation to establish a regulatory framework for in vitro clinical 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 small 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.

AAB and NILA appreciate the Committee's interest in identifying a viable solution to achieve fair regulatory oversight of laboratory developed tests (LDTs) and test kits. While AAB/NILA previously endorsed a policy that supports development of a new regulatory pathway under the FDA for high risk tests and oversight of moderate and low risk tests under a modernized CLIA, we understand the merit of the proposed approach being offered by the Committee. Compromise may be achievable, but for that to be possible, we believe there are gaps that must be addressed in the proposal as drafted to best ensure the safety and effectiveness of the tests and test kits to be reviewed. The primary purpose of a regulatory paradigm to oversee these tests and test kits should be to avoid potentially life-altering or life-threatening implications from an inaccurate or misleading test result.

AAB/NILA believe the following tenants must be addressed by the Committee's legislative draft:

- 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 and test kits should be through a risk-based approach that ensures both the analytic and clinical validity of all LDTs.
- Recalls of LDT tests and test kits should require re-classification of a test/test kit's risk level.
- CLIA can and must be modernized to support the post-market oversight of most LDTs, including, when necessary, a modified proficiency testing program for LDTs and test kits when they cannot undergo traditional proficiency testing.

Definitions

The draft legislation would add to the end of Section 201 of the Federal Food Drug and Cosmetic Act (FFDCA) [21 U.S.C.§321] a new section with newly defined terminology. This terminology includes in vitro clinical tests (IVCTs) and laboratory test protocols. While it seems from the definitions outlined that both laboratory developed tests and device test kits would be considered IVCTs, the definitions included in the draft do not clearly state this to be the case. Since laboratory developed tests are not currently referenced in statute, clarification of whether these tests are meant to be defined as IVCTs is warranted. Likewise, to avoid loopholes or confusion in regulatory oversight it is also necessary the legislation specifically address other types of laboratory tests including those newly defined in statute, namely Advanced Diagnostic Tests under Section 216 of the *Protecting Access to Medicare Act*. The legislation should clarify that the intent is to address the approval and oversight of both laboratory developed tests and advanced diagnostic tests.

Recommendation: Include the terms laboratory developed test, test kits, and advanced diagnostic tests in the definition of IVCTs.

Regulation of IVCT Development Activities

Practice of Medicine

The draft legislation rightfully acknowledges that IVCTs are not the practice of medicine and should not be regulated as such. However, the Committee is for the first time trying to federally define the practice of medicine and errs in doing so. The only criterion on the Committee's list that constitutes the practice of medicine is "(ii) Rendering a diagnosis as a result of specimen review." Each of the other criteria whether it is recommending appropriate in vitro clinical tests, interpreting data, discussing results with a health care provider, or assessing the output have all properly been performed by non-physician clinical consultants under CLIA for decades (42 CFR §493.1455). This distinction between the practice of medicine

and the work of clinical consultants for laboratories has also been upheld by federal courts. It is not necessary for purposes of this legislation to identify the practice of medicine and then declare it not subject to Secretary's regulation. To the extent, however, that it is determined to do so, the practice of medicine should be limited to item (ii) rendering a diagnosis as a result of specimen review" and should strike subparagraphs (i), (iii), (iv), and (v).

Recommendation: Under Sec. 590 Regulation of In Vitro Clinical Test Development Activities, (2)(B), the Committee must strike subparagraphs (i), (iii), (iv), and (v).

Classification of IVCTs

AAB and NILA support the establishment of a risk-based classification system toward developing the premarket review needed for IVCTs. There is precedent for such an approach with clinical laboratories as CLIA certification for laboratories is based on the level of complexity of testing that a laboratory performs: waived (low); moderate; high complexity. We support classifying tests as high, moderate, and low risk. We are concerned, however, that as structured in the draft, many tests would have no real requirement for establishing clinical validity and many other tests could inappropriately fall under the low risk classification. We are extremely concerned that the low risk classification has no formal premarket review requirements under the parameters of the draft legislation. The only requirement a manufacturer of a low risk IVCT must meet under the terms of the draft is a FDA notification requirement after the IVCT has already been made available to the public. The legislation must ensure that its structure does not establish a formal loophole for IVCTs to mostly default to a category that has no requirement for assessing a test's analytic and/or clinical validity. Ensuring the accuracy and reliability of low risk tests is paramount for patient safety and physician reliability, and also to ensure that such tests will be covered and reimbursed in the marketplace. Given the current scrutiny by Medicare and commercial payors who require evidence of performance before determining coverage and reimbursement of a test, Congress must establish a structure that ensures any IVCT is analytically and clinically valid.

One approach could be to establish varying requirements for tests deemed to be low risk depending on whether the test has a high or low volume threshold. The lower the volume threshold, the less risk to the public given the smaller number of individuals that would utilize the test. This could be particularly effective for tests addressing rare/orphan diseases, affecting a smaller population where innovation is so sorely needed and the burden of clinical trials to establish clinical validity could prohibit advancement of such testing. As low risk tests grow in volume, exposing a greater segment of the public to such testing, the low risk classification requirements could be altered to require additional studies and assessment.

Recommendation: Require moderate risk tests to establish clinical validity rather than "a reasonable belief of clinical validity;" impose premarket review requirements on low risk tests, varying those requirements based on a FDA-determined low-volume threshold.

Determining Test Risk Level

The draft legislation establishes advisory panels and public comment periods to support the classification of IVCTs that were lawfully introduced or delivered into interstate commerce before the date of enactment. The draft also allows for the use of advisory panels when an IVCT classification by the FDA is being appealed and when a test is being considered for reclassification. AAB and NILA also believe that because of the many challenges the federal agencies have currently had in defining risk in relation to laboratory developed tests, a formal process must also be established during the initial risk classification process. A formal federal advisory committee and rulemaking process should exist for review of an initial laboratory/manufacturer recommendation on how a given test or test kit is to be classified, rather than leave this initial determination up to the sole discretion of the FDA. Any new risk-classification review system 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.

Recommendation: For the premarket review process of IVCTs require the Secretary to establish an advisory panel to review and recommend the classification of tests and require the recommendations to be subject to public comment after publication by the Secretary.

Proprietary Algorithms

The risk assessment process outlined in the draft legislation must also consider the transparency of the test methodology utilized when assigning risk, 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. The draft legislation does not address these algorithms directly, despite them being addressed formerly in Section 216 of the *Protecting Access to Medicare Act*. The legislation does address and define "laboratory platforms," defining them as hardware or software intended by its developer to be used with one or more IVCTs to generate a test result. Clarification is needed as to whether platform is new terminology for an algorithm.

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. To establish the analytical and clinical validity of these highly specialized tests would inevitably require prospective studies that can demonstrate statistical relevance to prove that an algorithm works.

Recommendation: Tests that utilize proprietary algorithms should be classified as high or moderate risk and the legislation should require prospective clinical studies to demonstrate effectiveness and accuracy.

Post-Market Oversight of IVCTs

Proficiency Testing

AAB and NILA are extremely disappointed that the Committee's draft includes no system for external quality control or the post-market assessment of IVCTs. The only post-market requirements outlined in the draft legislation are for adverse event reporting, after a tragedy or other threatening event has occurred. AAB believes we can do better and structure a program that ensures against such adverse events. Post-market assessment of the quality of testing is paramount to ensuring the safety and efficacy of IVCTs that are being made available to patients. External quality control programs that currently exist through the CLIA-based proficiency testing program tell the agency how well laboratory tests are performing in the field. Over the years, this process has served to protect the interest of patients; it has not resulted in barriers to patient access to laboratory tests.

The current proficiency testing program must be modified in order to adequately assess IVCTs, namely LDTs and ADTs. Many of these tests may only be conducted by a single laboratory and the test result samples from that single laboratory cannot simply be tested in comparison to samples from other laboratories. A modified proficiency testing program under CLIA is needed to ensure that the testing results from a single lab can be replicated and shown to be accurate and reproducible.

AAB has developed the parameters of a modified proficiency testing program that in collaboration with CLIA could be structured to assess the validity of IVCT lab test samples. We encourage the Committee to require that the FDA, CMS and proficiency testing providers work to establish such a program upon enactment of the legislation.

AAB envisions a system where laboratories can provide IVCT lab test samples to an approved proficiency testing provider, and the proficiency testing provider will serve as an honest broker, de-identifying the sample and providing it as an unknown to a laboratory for testing. 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 proficiency testing 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.

A modified proficiency testing program for IVCT lab tests would be designed cooperatively by the laboratory and the proficiency testing provider. The proficiency testing provider would ensure that the program meets basic guidelines, and the laboratory would be responsible for designing a program that best assesses the accuracy of their method. The cost of such a modified proficiency testing program, like traditional proficiency testing programs, would be borne by the laboratories.

Recommendation: The legislation must include a post-market requirement for external quality control through proficiency testing. The legislation must require CLIA in collaboration with the FDA and outside stakeholders to develop a required modified proficiency testing program for IVCTs upon enactment.

AAB/NILA also believes that the Committee should ensure an improved system exists to guarantee the safety and efficacy of test kits the FDA is reviewing for "waived" status. Over the years, the FDA has demonstrated that regardless of current quality system requirements, 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 or recall. The legislation should seek to require such an assessment prior to a test being approved for waived status. For waived tests identified to risk public health, the tests should automatically be placed in a higher risk classification until such time they can demonstrate safety and efficacy.

Recommendation: Require that tests being considered for waived status first undergo proficiency testing to demonstrate safety and efficacy. Allow for waived tests found to have performance problems to be reclassified until safety and efficacy can be restored.

Adverse Event Reporting/Recall Authority/Post Market Studies

The draft legislation includes requirements for an IVCT developer to report adverse events, and for the Secretary to recall IVCTs or require additional post market studies for those IVCTs that cause or threaten risk or actual damage to patient health or result in death. AAB and NILA believe that (1) the legislation must go further and ensure that recalled tests and test kits are not re-branded by the manufacturer, laboratory, or a reseller and allowed back on the market; and (2) that tests and test kits that are being questioned for accuracy where the Secretary may deem it necessary to require additional post-market studies or other evaluation would automatically be classified for a defined period of time into a moderate or high-risk test category, even if that test had previously served in another (and lesser) risk classification. Tests or test kits that are recalled or scrutinized for post market re-evaluation should automatically be required to undergo proficiency testing to ensure quality of the tests/kits.

Recommendation: The legislation must provide the FDA the authority to reclassify IVCTs into a higher risk classification if the test is believed to threaten the public's health until such time the IVCT is proven to be safe and effective.

Laboratory Operations

CLIA Modernization

Current CLIA requirements for proficiency testing for specific specialties and subspecialties have not been updated in over 20 years, lagging far behind today's current laboratory testing. The list of specialties/subspecialties must be broadened to cover all categories of laboratory testing not currently included in CLIA's list of covered analytes (e.g., genetic testing). To ensure that CLIA continues to keep pace with the evolution of laboratory tests into the future and protects the public's health, the legislation should require that CLIA update the list of regulated analytes no less than every five years.

The recent Ebola crisis and efforts to approve and assess the quality and effectiveness of new tests to identify Ebola diagnosis emphasize the shortcomings of the current CLIA process. Today, there is no requirement to independently assess an Ebola test under CLIA. Because the list of specialties/subspecialties under CLIA are so limited and CLIA only looks at such things as bacterial antigens and viral antigens, if an Ebola test is a viral antigen-based test, the laboratory that developed the test satisfies current CLIA requirements through other viral antigen programs (e.g., influenza), and no proficiency testing is required on the Ebola test. This is happening today, and putting the public's health at serious risk.

Recommendation: Require CLIA to update the list of regulated analytes no less than every five years. Stakeholder input should be required to update the current list of specialties and subspecialties under CLIA.

FDA Fees

AAB and NILA are concerned about what new user fees may be required to sustain establishment of a new FDA Center and regulatory pathway for the broad category of IVCTs as defined in the draft legislation. An assessment should be conducted by Committee to see the variance in cost of establishing such a new process for LDTs identified as IVCTs versus LDTs and laboratory test kits, given that the latter are already regulated and paid for under the FFDCA and with existing user fees. AAB and NILA also want to ensure that no new user fees are applied to those clinical laboratories that do not perform LDTs or other types of tests that would be deemed IVCTs. Such laboratories should not be asked to subsidize the cost of a new regulatory system for tests they do not perform.

Conclusion

Thank you again for the opportunity to comment on the draft legislation. We look forward to continuing to work with you as you address issues related to the regulation of laboratory developed tests. We would be pleased to meet to discuss our comments in further detail and answer any questions. For more information, please contact Julie Scott Allen, our Washington representative, at (202) 230-5126 or julie.allen@dbr.com.

Sincerely yours,

Mark S. Birenbaum, Ph.D.
Administrator