



**ASSOCIATION FOR MOLECULAR PATHOLOGY**

*Education. Innovation & Improved Patient Care. Advocacy.*

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April 7, 2017

The Honorable Larry Bucshon  
1005 Longworth House Office Building  
Washington, DC 20515

The Honorable Diana DeGette  
2111 Rayburn House Office Building  
Washington, DC 20515

Sent via e-mail: [Jeffrey.Lucas@mail.house.gov](mailto:Jeffrey.Lucas@mail.house.gov); [Polly.Webster@mail.house.gov](mailto:Polly.Webster@mail.house.gov)

Re: Diagnostic Accuracy and Innovation Act

Dear Representatives Bucshon and DeGette:

Thank you for the opportunity to comment on the draft legislation “Diagnostic Accuracy and Innovation Act.” We appreciate your willingness to engage stakeholders and for the time and effort that you and your staff have devoted to this important issue.

The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who develop, perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from academic medicine, commercial and community hospital-based testing laboratories, the government and the in vitro diagnostics industry. It is one of the goals of our organization to ensure that patients have access to innovative and high quality laboratory testing procedures. As you continue your work on this draft legislation, AMP welcomes the opportunity to provide you with resources and input from our expert members.

AMP has been significantly engaged in conversations on laboratory developed testing procedures (LDPs) for many years, and we support addressing safety concerns and enhancing transparency while maintaining patient access to reasonably-priced and innovative testing. In order to assist in those efforts, clarify expectations, and in support of AMP’s dedication to patient care and innovation in the field of molecular pathology, AMP’s experts held numerous discussions, incorporated feedback from many other stakeholders, and developed a [proposal](#) to modernize the Clinical Laboratory Improvement Amendments (CLIA) program at the Centers for Medicare & Medicaid Services (CMS). This proposal was shared with the Energy and Commerce Committee in 2015, and we invite you to review this document as it was endorsed by numerous organizations, academic institutions, and molecular pathologists. **AMP maintains that a CMS-based system of oversight for LDPs is the key to enhancing standards and transparency while preserving innovation, minimizing cost and regulatory burden, and protecting the practice of medicine.**

AMP does not believe that the Food and Drug Administration (FDA) is the appropriate agency to regulate LDPs. Our professional members provide medical services. They do not manufacture products. Manufacturing products for sale and providing a medical service are fundamentally different activities. Furthermore, when substantial improvements in standards for LDPs can be made through an existing mechanism, we do not believe that the burden associated with FDA review, in addition to resources required to create a new center at FDA, is warranted.

As [relayed to the Energy and Commerce Committee previously](#), AMP believes that reform of regulation of manufactured distributed test kits is needed. Current regulations imposed by FDA significantly hamper the ability of manufacturers to modify, enhance, or improve commercial kits. Clinical laboratories are eager to use FDA-reviewed commercially available test kits that can assist them in patient care, but those kits must be properly validated, clinically relevant, and cost effective. The FDA-cleared MiSeqDx Cystic Fibrosis Clinical Sequencing Assay exemplifies both test limitations and how test modifications are inhibited for an in vitro diagnostic (IVD) test. The intended use of this IVD is narrow and thus needs to be frequently adapted by performing laboratories to meet their patient's specific needs. However, clinical study regulatory issues and other limitations, including difficulty in obtaining samples for test development, inhibit IVD manufacturers from expanding indications for which their test can be used. Transferring an FDA regulatory burden to clinical laboratories will not solve this problem and will limit their ability to provide needed testing for their patients.

Even if those issues were remedied, commercial test kits could never meet all patient care needs, and LDPs are an invaluable service that must be readily available to provide patient care in all aspects of medicine, including oncology and emerging biothreats. The proposed legislation reduces regulation on commercially distributed tests while drastically increasing the regulatory burden on laboratories and medical professionals. It also shifts much of product liability from manufacturers to clinical laboratories and medical professionals. This draft legislation could cripple clinical laboratories of all sizes, including major cancer centers and public health facilities, and in the process, thwart the provision of essential patient care. **As such, AMP cannot support this draft legislation as long as it includes FDA regulation of LDPs.**

### **Core Principles of any LDP Regulatory Framework**

To better evaluate the numerous proposals circulated on the regulation of LDPs, AMP developed a set of [core principles](#) and used them as the foundation for the comments on the draft Diagnostic Accuracy and Innovation Act (DAIA). Below is a synopsis of how the draft legislation compares to AMP's principles and other proposals.

AMP understands that the intended goal of the draft legislation is to streamline oversight; however, the draft legislation requires that clinical laboratories and medical professionals behave as both healthcare professionals and FDA-regulated product developers. Submitting LDPs for premarket approval by the FDA would require an exorbitant level of financial and administrative resources that are unachievable for most clinical laboratories, particularly those based at academic and community medical centers (Principle 2). The draft legislation also would require healthcare professionals to consider their additional liability as product developers (Principle 8). The totality of costs associated with being FDA-regulated would force laboratories to stop improving a large portion of their services or close down entirely, resulting in a constriction of the market, which would severely hamper clinician access to critical expert consultations, and in many cases, patient access to these vital medical services. Concentrating testing to a few large laboratories that are far removed from patients and ordering physicians would disrupt traditional healthcare teams comprised of pathologists, geneticists, oncologists, and other health care providers. Additionally, it would disrupt training of the next generation of precision medicine providers.

We hear our friends in the patient advocacy community when they express general concerns about accuracy, clinical relevance, and standardization across laboratories, and we understand that patients have a great deal of trust in FDA's oversight because of their longstanding role in evaluating safety and effectiveness in drugs and traditional devices. However, the draft legislation will not adequately address many of those concerns (Principle 1), and in the process will apply a new and additional layer of regulation on LDPs. AMP believes that these concerns can be fully addressed through the processes outlined in our CLIA Modernization proposal. Laboratories are well-versed in the requirements of the CLIA program, which ensures that laboratory personnel and the examinations they perform can accurately and precisely detect biomarkers of interest. Furthermore, the clinical relevance of those biomarkers are most often well validated through peer-reviewed publications or by practice guidelines. Third party reviewers, like the kind proposed in the draft legislation, already are in widespread use and the mandates that provide the minimum threshold for their work can be adjusted to require "premarket" (i.e. pre-introduction) review, collection of data on clinical validity, and lab to lab comparisons. FDA is not equipped to foster test to test comparisons, and we believe that this is an important aspect of the success of the CLIA program.

AMP has proposed that all LDPs be subject to proficiency testing, as does the draft legislation; however, AMP's 2015 proposal also seeks to incentivize comparative testing. We believe that FDA can serve an important role in the field by assisting in the development of reference materials (Principle 16), and we welcome thoughts on how Congress can support FDA in that role. Moreover, AMP believes that transparency in performance specifications and the evidence associated with clinical relevance will go a long way towards helping treating physicians and patients appropriately select the best procedure for each specific situation. We encourage draft legislation that tasks CMS to work with professional organizations to create a database that serves this purpose (Principle 14).

Unlike manufactured, packaged, and distributed IVD test kits, LDPs are a medical service, which encompasses the design, validation, performance, ongoing monitoring, and interpretation of test results (Principle 3). Professional judgment is used throughout the provision of these services, providing continual opportunities to promote test accuracy, reliability and patient safety. For an LDP, a defining aspect of quality is the direct involvement of an appropriately qualified medical professional in every aspect of the testing service including ongoing assessments and adjustments necessary for the unique context of the individual laboratory and patients that they serve. This distinguishing feature of all LDPs is not at all incorporated into the draft legislation. While this could easily be adopted as a risk mitigating measure in the legislation, it would not address the inappropriate application of oversight based on "activity regardless of entity type." The activities associated with developing an LDP differ from that of an IVD in some crucial ways, including the design for certain intended users, their applications, and involvement of the medical professional in constant monitoring activities. The draft draws an artificial line that assigns regulation of "developing" an LDP to FDA, while placing oversight of "performance" of an LDP within CLIA. With LDPs, development cannot always be clearly and consistently distinguished from performance. Therefore, actual implementation of the proposed regulatory structure contained within the draft legislation would be confusing for professionals, laboratories, and the agencies as it would not be clear which Agency's rules would govern under specific circumstances. Further, the activities associated with LDPs are encompassed under the practice of medicine and the draft legislation seeks to widely expand FDA's jurisdiction to include medical activities (Principle 4) while reducing regulation on the tools used in our members' professional practice.

Much of our members' work relies upon the use of peer-reviewed evidence which serves the public in identifying analytic and clinical limitations of some tests and improving upon LDPs that would otherwise become quickly outdated under FDA's purview. Without the ability to review the data that a test relies upon, the public cannot benefit from this additional layer of certainty. AMP has provided our definition of the highest

risk test in the principles chart (see Principle 3). In summary, it is a test used to predict risk or risk of progression of a life-threatening disease and uses methodologies that involve proprietary algorithms or computations. AMP believes that transparency is a critical component of how much risk a test presents to a patient. When a test uses proprietary methodology, the test cannot be easily evaluated by the broader community of appropriately trained professionals. AMP believes that third party review is warranted for such tests. This feature is not addressed in the draft legislation's risk classification system (Principle 5).

AMP believes that the flexibility of the current regulation system for LDPs is an asset to patient care in that it allows for LDPs to be quickly updated (Principle 11). We appreciate that the draft legislation seeks to improve the review time at FDA for modifications to IVDs. However, the draft legislation would decrease the current regulatory flexibility for LDPs by severely limiting the ability of laboratories to modify and improve LDPs (see Principle 10). AMP is particularly concerned that the draft legislation does not acknowledge that changing the specimen types for testing is a common practice and often necessary test modification. The draft legislation leaves the requirement for FDA review regarding a specimen type addition to an Agency assessment of practice and "meaningful clinical impact," which is vague, and "changes the intended use," which in many instances could force a submission since specimen types are included in the intended use statement. Any regulatory framework should allow flexibility with regards to sample type when relevant and we encourage you to adjust the draft legislation to reflect this.

Furthermore, if the draft legislation seeks to break away from the traditional FDA device pathway then AMP also suggests that the legislation move FDA away from the single test, single drug paradigm as described by the term "companion diagnostic." This approach is obsolete as new technologies allow for the testing of multiple analytes simultaneously with greatly reduced per-analyte costs (Principle 6).

The adverse event requirements in this draft legislation are very similar to what is required by the current FDA medical device regulations. We believe compliance with these requirements is likely to consume significant administrative resources without accompanying benefits to patient care or gains in patient safety (Principle 1 and 2). Our members' experience performing hundreds of thousands of laboratory tests (including LDPs) over several decades suggests that the risk of LDPs causing or contributing to a death or serious injury, as defined by the draft legislation, is exceedingly low. In addition, CLIA already requires labs to report to ordering physicians errors in test results (Principle 7).

The draft legislation adverse event requirements would necessitate that laboratories develop an additional and duplicative policies and procedures for reporting adverse events as well as an additional infrastructure to analyze potential adverse events, including maintenance of records of investigations and analyses. It is already required that laboratories have systems in place that evaluate *all* failures and include an assessment of the impact on patients. Based on the already collected information, the overwhelming likelihood is that the extensive additional administrative burden molecular professionals would be subject to would not yield any reportable events. AMP believes that it is far more important for CLIA regulations to be updated to include a focus on preventing errors associated with laboratory processes, which are more likely to lead to problems with regards to patients receiving misinformation about their clinical presentation. AMP recommends that adjustments be made to the CLIA regulations to enhance reporting abilities and transparency of the reported information. AMP's proposal addresses adverse event reporting in a manner consistent with the operation of a clinical laboratory rather than a manufactured IVD, utilizing realistic standards based on effects of laboratory test results on patients. If the draft legislation is going to address updating CLIA we believe that it should aim to increase transparency about laboratory/LDP errors and require laboratories to have ready access to a mechanism that enables ordering physicians to report possible laboratory/LDP errors (Principle 9).

There is a great deal of work being done outside of the federal government to enhance molecular and genetic testing. AMP believes that federal regulations should not disrupt the success of the New York State Department of Health Clinical Laboratory Evaluation Program. States that currently have exempt status under CLIA should continue to have exempt status under any new framework.

Additionally, AMP encourages you to further consider how the ongoing work of professional societies can fulfill some of the activities outlined in the draft legislation. AMP has been busy the past year collaborating with other professional organizations to develop and publish consensus guidelines and standards for molecular testing - most recently on:

- [Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer](#), and,
- [Molecular Biomarkers for the Evaluation of Colorectal Cancer](#).

AMP believes it is the responsibility of professional organizations to establish guidelines for professional practice and as such we routinely engage with other professional associations such as the American College of Medical Genetics and Genomics, the College of American Pathologists, and the American Society of Clinical Oncology to publish evidence-based practice guidelines. We appreciate that the draft legislation incorporates the use of practice guidelines in its determination of “well-characterized,” but feel that their significant role in the field should be further utilized. For example, AMP is conducting a special initiative to help achieve uniformity in variant classification across laboratories using next generation sequencing technology. These standard-setting efforts enable the field to continue to develop high quality testing procedures. We encourage Congress, FDA, and CLIA to support this work rather than creating additional regulations in an effort to achieve the same goal.

In conclusion, AMP has considered the desires of treating physicians and patients and believes that all stakeholders have the same ultimate desired outcome: that laboratory testing procedures be high quality, accurate, and precise. We encourage you to explore AMP’s principles as they relate to the draft DAIA, AMP’s 2015 proposal, and other frameworks more fully. For your convenience, we have attached a copy. We are committed to the advancement of molecular diagnostics to inform medical care by holding ourselves to high standards and working with Congress and the Administration in that pursuit. Thank you again for the opportunity to submit these comments on this draft legislation. AMP looks forward to working with you and federal agencies to design modernized regulations for LDPs that ensure both analytical and clinical validity as well as provide the nimbleness necessary to foster innovation and enable patient access to appropriate testing. If you have any questions or if AMP can be of further assistance, please contact Tara Burke at [TBurke@amp.org](mailto:TBurke@amp.org).

Sincerely,

Federico A. Monzon, MD  
President, AMP