



**ASSOCIATION FOR MOLECULAR PATHOLOGY**

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

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June 22, 2015

The Honorable Fred Upton  
Chairman  
House Energy and Commerce Committee  
2125 Rayburn House Office Building  
Washington, DC 20515

The Honorable Frank Pallone, Jr.  
Ranking Member  
House Energy and Commerce Committee  
2125 Rayburn House Office Building  
Washington, DC 20515

Sent via e-mail: [RobertHorne@mail.house.gov](mailto:RobertHorne@mail.house.gov); [tiffany.guarascio@mail.house.gov](mailto:tiffany.guarascio@mail.house.gov)

Re: Regarding the draft legislation on the regulation of in vitro clinical tests

Dear Chairman Upton and Ranking Member Pallone:

Thank you for the opportunity to submit comments on draft legislation that would create a new regulatory pathway for in vitro clinical tests. As you know, the Association for Molecular Pathology (AMP) has met with both your staff and provided feedback numerous times since the 21st Century Cures Initiative was launched last year. We appreciate your willingness to continue working towards policies that best ensure that patients have access to innovative and accurate laboratory tests and look forward to a continued collaboration with you and your staff.

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 the government, academic medicine, clinical testing laboratories, and the in vitro diagnostics industry.

AMP's position statement on the oversight of laboratory developed testing procedures (LDPs) supports enhancing CLIA regulations to modernize the current oversight practices. AMP does not believe FDA is the appropriate agency as our clinical practice members provide a medical service, not manufacture a product.

AMP believes that reform of regulation of manufactured distributed test kits is needed. The current regulations imposed by FDA significantly hamper the ability of manufacturers to modify, enhance, or improve commercial kits. Clinical laboratories are eager to use commercially available test kits but they must offer current clinical relevance and cost effectiveness. However, commercial test kits can never meet all patient care needs; LDPs must be readily available in order to provide patient care in all aspects of medicine, including oncology and emerging biothreats. The proposed legislation reduces regulation on 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. It cannot be stated strongly enough: medical care begins with an accurate diagnosis. Both FDA's proposed framework for oversight of LDPs and this proposed 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 legislation and these comments summarize our concerns.

## **Goals of a Regulatory Oversight Proposal:**

AMP members and the services they provide to patients are the foundation of the healthcare system. At the core of these health care services are LDPs, also known as laboratory developed tests. Molecular diagnostics now enable physicians to understand a person's disease and tailor treatments in an unprecedented manner and their role in medicine will only continue to grow as personalized medicine advances. AMP is currently working on its own proposal for oversight of LDPs and hopes to share that with you and your colleagues later this month.

With the understanding that this is an important issue, AMP developed a list of goals for any oversight process:

- Patients receive the most appropriate LDP(s) for their clinical condition.
- LDPs are accurate, precise, and clinically relevant.
- Health care professionals are able to provide professional services without undue restrictions.
- Regulatory oversight does not slow innovation, constrain flexibility and adaptability, or limit a test's sustainability as a result of being unduly burdensome and overly expensive.

AMP is pleased that the draft legislation keeps LDPs outside of the medical device regulatory framework, which restricts innovation and reduces the incentive to update tests when scientific advancements are made. A laboratory's nimbleness and ability to modify a test to meet a patient's clinical needs is a critical aspect of medical care. Additionally, the legislative proposal dramatically decreases review times at FDA and makes the level of evidence more appropriate and reasonable for in vitro diagnostic (IVD) kits. AMP is pleased that the proposal also provides opportunities for stakeholder engagement through advisory panels. Last, AMP believes the grandfathering provision could reduce the regulatory burden on laboratories and FDA.

However, AMP believes that the draft legislation would work in opposition to these goals as it was not developed from the perspective of maintaining patient access to innovative and accurate tests. The legislation provides the same regulatory oversight for both boxed-and-shipped manufactured test kits and LDPs, which results in increased regulatory burden for laboratories and reduced regulation for manufactured, distributed test kits. Shifting regulatory burden from manufacturers of distributed test kits to laboratories and medical professionals would result in laboratories being forced to stop improving tests or would remove them from patient care altogether. AMP understands that there may be a small number of high risk laboratory tests that warrant increased scrutiny; however, there are less burdensome ways to ensure that patients receive accurate, precise, and clinically relevant tests than what is described in this draft legislation. The legislative proposal fails to acknowledge that a laboratory professional's involvement in every step of designing, validating, performing, and interpreting an LDP inherently mitigates risk. These activities are a part of their professional practice and are regulated by the states and the requirements of existing accreditation and quality programs. It is not appropriate that they be subject to the same regulations as the manufacturer of a boxed-and-shipped diagnostic test kit.

Most laboratories do not have the financial and administrative resources required to submit their tests for FDA review, even for the FDA process outlined in this proposal. It is worth noting that manufacturers are able to shift increased costs due to increased regulation to their customers, i.e., laboratories; however, laboratories and medical professionals have no mechanism to offset the increased costs that the proposed legislation makes certain for them. Payment for most laboratory tests performed in hospitals is already bundled into diagnosis related payments, and this trend is expected to continue going forward. Molecular testing is in a unique situation of non-coverage and poor reimbursement. The combination of precipitously increasing costs and plummeting coverage and payment threatens broad patient access to clinical services that are standard of care.

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

In order to provide more specific feedback on proposals, AMP developed a list of principles that any regulatory framework should meet with regards to the oversight of LDPs and evaluated how well the draft legislation

addresses each of them. This principles chart is enclosed for your reference. As you can see, the draft legislation fails to meet ten of those principles and only partially meets the remaining six. To accompany the chart, we provide more comprehensive responses to a select list of issues below.

This legislative proposal will increase the regulatory oversight of LDPs, and consequently, the regulatory burden for hospitals, cancer centers, public health laboratories, physicians and other doctoral laboratory professionals, to name but a few. Yet, the need for increasing oversight has not been adequately described and supported with data and therefore, it is unclear what systemic problems in laboratory practices the legislation intends to address. Understanding the problem is a key component to determining the appropriateness and need for any increase in regulation. AMP believes that any proposed legislation or regulation should clearly define the problem to be solved through regulatory action, be able to quantitatively assess the problem, show that the proposed regulatory action will address the problem, and demonstrate that the regulatory burden outweighs the societal costs imposed by the problem (see Principle 1). The Committee should undertake such a process first to ensure their proposal provides a reasonable and appropriate solution.

AMP believes that the draft legislation inappropriately defines each risk classification. AMP has provided our definition of the highest risk test in the principles chart (see Principle 3), but 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 appropriately trained professionals and third party review is warranted. We are appreciative that there is flexibility in the risk classifications within the proposed legislation to allow for a test to move to a lower risk category as a test becomes better characterized; however we believe that the vast majority of tests are not in this highest risk category and should not be subject to premarket review (see Principle 5).

The draft legislation would severely limit the ability of laboratories to modify and improve LDPs because it requires that a test be resubmitted for further review (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 decision regarding whether adding a specimen type would be subject to FDA review to an 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 necessary and the draft legislation should reflect this.

In almost all cases, third party pre-market review is unnecessary when modifications are made to an LDP or when an LDP is validated for a different specimen type (see Principle 10 and 11). Supplemental premarket submissions should only be required for those tests for which premarket review by a third party is required, i.e., the highest risk tests as defined in AMP’s principles chart, and should not be based on intended use.

The draft legislation requires that, as a condition of test approval or listing, the developer of an LDP keep a record on any adverse event that is known to the developer. The record would have to contain all documentation of the developer’s deliberations used to determine whether a test error needed to be reported to CMS. In addition, a report would have to be submitted to CMS within 15 calendar days after the adverse event becomes known to the developer if the adverse event involves an actual patient death or presents an imminent threat to public health. These requirements are very similar to what is required by 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 (See Principle 1 and 2). Our members’ experience performing thousands of laboratory tests over many years suggests to us that the risk that the vast majority of LDPs would cause or contribute to a death or serious injury, as defined by the draft legislation, is exceedingly low. In addition, CLIA already requires labs to report errors in test results to ordering physicians.

Despite the low likelihood of contributing positively to patient care, these requirements would necessitate that laboratories develop policies and procedures for reporting adverse events as well as an infrastructure to analyze potential adverse events, including maintenance of records of investigations and analyses. Although the costs of establishing and implementing processes and procedures, as well as the documentation ongoing analyses would require are non-trivial, the overwhelmingly likelihood is that the extensive surveillance our members would need to pursue would not yield any reportable events. AMP believes that 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.

The draft legislation does not make many of the necessary updates to the CLIA regulations (see Principle 9). CMS's list of regulated analytes is outdated and does not include many analytes that are routinely used in standard patient care. CLIA should have a mechanism that involves area experts through which the list of regulated analytes is updated on a regular basis. In addition, there are various ways to enhance accountability of proficiency testing programs and information flow between laboratories, treating physicians, and patients (see Principle 14). As previously stated, we are working on specific recommendations to present to the Committee in the near future.

Additionally, AMP is very concerned about the potential way the agencies would interpret the proposed legislation and the possible resulting regulation could be highly detrimental to patient access and professional practice. We list examples below that are of significant concern to AMP.

- A test would be considered high risk if it met four criteria including when a wrong result is likely to have a “significant impact” on patient outcome or public health. It is unclear what FDA would consider a “significant impact.”
- The draft legislation leaves quite a bit to be determined by CMS in the future with regards to updating standards, especially considering that laboratories would be expected to adopt elements currently in FDA QSRs, *e.g.*, purchasing controls, many of which are not applicable to clinical laboratories or almost impossible for them to achieve.
- A laboratory would be expected to notify FDA before a low risk test is introduced, however, draft legislation does not define what it means for a test to be introduced.
- With regards to the review of a moderate risk test, it is unclear what it means for there to be a “reasonable belief” that a test is clinically valid. AMP believes addressing clinical validity is best accomplished by updating current CLIA regulations and recommends that CLIA is modernized with the input of professional societies to develop evidentiary standards with regards to clinical validity. The draft proposal does not define the kind and amount of evidence required to establish clinical validity. We presume FDA would apply requirements currently in force for manufactured and distributed tests, which, as we have noted, are not appropriate for LDPs and are not necessary to ensure that LDPs are accurate, reliable, and clinically relevant.
- Under submission requirements in Section 6, the draft legislation does not address what would be required of developers for tests developed before the bill's enactment.
- The draft legislation establishes a new FDA center, which would require significant funding requirements. We are concerned that FDA does not currently have sufficient resources to undertake this task without slowing down the review of medical products or jeopardizing its other functions. AMP believes that a targeted approach to modernizing the CLIA regulations is both a more effective and more responsible use of public funds.

Last, under the grandfathering section (pg. 33, line 6) the word "data" should be changed to "evidence." Health care professionals may not have ready access to raw data, but would have access to peer reviewed scientific literature which should be sufficient, if certain criteria are met, to demonstrate clinical validity.

Thank you again for the opportunity to submit these comments on this draft legislation. AMP looks forward to working with the Committee 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 Mary Williams at [mwilliams@amp.org](mailto:mwilliams@amp.org) or 301-634-7921.

Sincerely,

Janina A. Longtine, MD  
AMP President