



ASSOCIATION FOR MOLECULAR PATHOLOGY
Education. Innovation & Improved Patient Care. Advocacy.
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August 24, 2018

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

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

The Honorable Orrin Hatch
104 Hart Senate Office Building
Washington, DC 20510

The Honorable Michael Bennet
261 Russell Senate Office Building
Washington, DC 20510

Re: Comments on FDA's technical assessment of the Diagnostic Accuracy and Innovation Act

Sent electronically to: Sarah.Killeen@mail.house.gov; Michelle.Greenhalgh@mail.house.gov;
lauren_paulos@hatch.senate.gov; Rita_Habib@bennet.senate.gov

Dear Representatives Bucshon and DeGette, and Senators Hatch and Bennet:

On behalf of the Association for Molecular Pathology (AMP), thank you for the opportunity to submit the following comments on the US Food and Drug Administration's (FDA) technical assessment on the discussion draft of the Diagnostic Accuracy and Innovation Act (DAIA). In particular, we are grateful that you invited the voice of our members into this important conversation.

AMP is an international medical and professional association representing approximately 2,400 physicians, doctoral scientists, and medical technologists who validate, 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.

AMP maintains that any regulatory proposal for laboratory testing should be given careful and thoughtful consideration by all stakeholders and relevant agencies. This issue is multifaceted and deserves a thorough understanding of how proposed requirements would affect medical innovation, clinical laboratories, and patient access.

AMP greatly appreciates the time and effort that your offices have spent on exploring ways to modernize regulatory policy for laboratory tests; however, given the incompleteness of input by relevant agencies and the short review period provided, AMP looks forward to additional opportunities to provide comments once we have had the opportunity to study FDA's technical assessment with our members in more depth and when additional information is provided by Centers for Medicare and Medicaid Services (CMS). It is possible that upon further review, AMP will identify additional questions

and concerns. Thus, the comments below represent preliminary thoughts and concerns on the FDA proposal that we hope will be useful as you digest the document.

FDA Proposal Lacks Clarity

AMP believes that any new framework should not deter the advancement and adoption of personalized medicine. Thus, it is important that proposed frameworks clearly outline the new requirements, timelines, and process for laboratories and the relevant agencies. To that end, we are concerned that there are numerous instances where FDA's recommended language introduces additional lack of clarity for laboratory test regulations. In addition to the several high priority areas outlined in this letter that require further understanding, AMP asks that you seek clarification from FDA on their thinking and remedy all drafting errors and timeline placeholders.

Moreover, FDA's proposed language gives wide discretion to the Secretary, which creates even more uncertainty and raises concerns that a reasonable proposal may become overly restrictive and burdensome if interpreted in a restrictive sense and/or could drastically change over time.

Unique Aspects of Laboratory Developed Testing Procedures

AMP believes that there is a need to modernize regulations of both laboratory developed testing procedures (LDPs) and *in vitro* diagnostic (IVD) test kits; however, AMP remains concerned that establishing a single regulatory pathway for both IVDs and LDPs would never meet the needs of either as they are fundamentally different from each other. While the FDA proposal differs significantly from DAIA, one similar construct is that both proposals create a single regulatory pathway for both IVDs and LDPs. The discussion draft of DAIA lowered the regulatory threshold for manufactured test kits and platforms that are shipped for use by any clinical laboratory, including those whose personnel does not have the level of expertise in molecular testing possessed by medical professionals who design and validate LDPs. Conversely, regulatory oversight was greatly increased for LDPs, where the medical professional is an integral part of the design, validation, and interpretation of the test, which mitigates a great deal of risk to the patient. Similar to DAIA, FDA's proposed language does not factor the role of the medical professional into their framework. AMP urges you to incorporate language that considers the involvement of the medical professional and the expertise and experience of the laboratory's personnel with testing methodology as a risk reducing factor. Moreover, AMP believes that IVD test kits and LDPs should be regulated under two distinct pathways and does not believe that FDA is the appropriate agency to oversee the vast majority of LDPs.

AMP maintains that a CMS-based system of oversight for LDPs is the key to enhancing standards and transparency while protecting patients, preserving innovation and the practice of medicine, and minimizing cost and regulatory burden. However, AMP also recognizes the concerns by manufacturers of the current regulatory paradigm and supports regulatory efforts at FDA to streamline existing pathways for IVDs. AMP members readily use IVD test kits, when medically appropriate, and support predictable and streamlined regulation by FDA for those who manufacture boxed and shipped test kits and test platforms. We encourage you to draft legislation that modernizes IVD test kit oversight to provide greater certainty and more streamlined approaches for companies and FDA. This could actually decrease the need for molecular diagnostics professionals to use their own LDPs because manufacturers would have the regulatory flexibility to quickly respond to scientific discovery. Overall, a two-pathway system for IVD test kits and LDPs should be developed and adopted. AMP would welcome the opportunity to work with staff on legislation to do so.

FDA Jurisdiction over Laboratory Operations

FDA stated in their technical assistance released in April of 2018 that DAIA's approach would create parallel regulatory structures under CLIA and FD&C Act for similar activities. However, upon initial review of the FDA proposal, AMP also identified duplicative regulatory requirements for laboratory operations. AMP finds that the FDA-recommended language relating to the definitions of an *in vitro* clinical test, premarket review application, and quality system requirements would give FDA jurisdiction over many aspects of laboratory operations and overlaps with CMS activities authorized by CLIA. It is critical that clear lines are drawn between each agency's jurisdiction and that the successful programs and third-party systems that have resulted from CLIA are safeguarded. AMP believes that the best way to ensure this clarity is for IVD test kits and LDPs to be regulated under two distinct pathways, with oversight of the vast majority of LDPs under a modernized CLIA and not FDA.

Risk Classification System

AMP seeks to understand fully the two-tiered risk classification proposed by FDA. Upon initial review, there is uncertainty regarding which tests would fall within each category. Further, AMP is concerned that a two-tiered system may result in a large number of tests falling within the high-risk category when this is not necessary to ensure patient safety. AMP's CLIA modernization proposal includes a three-tiered risk classification and believes that this allows regulatory requirements to be precisely applied to laboratory tests to better protect patients and more appropriately use pre-introduction review exemptions and provisional approvals. Additionally, AMP believes the risk classification system offered by FDA should be revised to consider transparency of test methodology, the resulting impact on the ability for external parties to verify laboratory reported information, and the ultimate impact to the patient. We seek additional information and clarification from FDA on their proposed classification system, most importantly to understand exactly what tests or types of tests would fall within their high-risk category.

Professional Practice and Test Development Based on Patient Need

The proposed language offered by FDA also restricts a molecular professional from fulfilling their duty to a patient, which is aided by their ability to work collaboratively with their peers and tailor a test to meet the needs of both patients and the laboratory, not for commercialization purposes. Molecular professionals engage in these activities for the purpose of providing the best care possible to their patients. We outline several points and examples below to address how we believe FDA's proposal will prevent healthcare professionals from providing care to patients.

In many situations an FDA-approved or –cleared assay for certain specimen types does not exist and as a result, laboratories revalidate a test to accommodate other specimen types, often obtained using less invasive procedures. In FDA's proposed system, laboratory professionals would likely have to wait for a test developer to make this update and submit for approval before having access to a test that better meets the needs of their patients. As written, the proposal does not offer an incentive for developers to update their tests or achieve FDA approval for each relevant specimen type, even if a company could bear the cost of the initial FDA review. It is often the case now that LDPs are the updated and improved version of IVD test kits. By preventing molecular professionals from revalidating tests to incorporate scientific advancements or to comply with new practice guidelines, AMP is concerned that patients would be denied access to improved testing, potentially indefinitely. Instead, FDA's proposal could curtail best medical care and the adoption of personalized medicine.

An example of language in FDA’s technical assessment that would present problems for the creation of tests that meet patient need is the restrictive definition of the term “test group” which prevents the application of mitigating measures and standards that could be applied in a scientifically sound way to related tests. The result of this language would be that similar tests that fall just outside of the overly restrictive test group would not be able to rely on mitigating measures and standards to aid in their approval or qualify them as low risk and thus exempt from premarket review. To further illustrate this point, see *Section 587E Mitigating Measures (b)*. Under this section, the Secretary may require any test within a test group to comply with a mitigating measure. This could benefit tests included in the test group because mitigating measures could render a test as low risk and thus exempt from premarket review. However, if the specimen type is different than how the test group is defined, then those mitigating measures would not automatically apply and a test might not meet exemption status.

Additionally, FDA made use of a restrictive definition of “custom” *in vitro* clinical test. The criteria of a genetic test designed for certain “unique pathology or physiological condition” is too restrictive. Often, currently available IVDs approved to test for a particular condition fail to include all relevant analytes or biomarkers that may be associated with a set of symptoms for a unique clinical situation. Beyond the association with a condition, other factors such as technology and platform capabilities, clinical presentation, unknown variants, sample quality, etc. may indicate the need for a custom *in vitro* clinical test.

There is great push from policymakers and stakeholders for coordinated care; and, patients faced with complex conditions greatly benefit when their care providers coordinate with one another and are fully informed. Molecular professionals are a critical component of this clinical care team. FDA’s proposed language under the *Section 587A. Applicability (a)(3)* would severely limit the ability of a molecular professional to have conversations with treating clinicians about the merits and limitations of using certain types of testing for a particular patient. It is clear that FDA intends to prevent discussions about testing for other intended uses even in cases in which the information conveyed by the pathologist is neither false nor misleading. FDA’s proposed language would remove molecular professionals from these communications and is antithetical to the type of coordinated care system that policymakers and stakeholders are working to advance. It would prevent conversations that would aid the treating healthcare professional in selecting testing most appropriate for their patient. Furthermore, it would prevent the identification of test modifications needed to better accommodate patients. For these reasons, we urge you to adopt a legislative proposal that would fully protect the professional activities of medical professionals in the laboratory.

Incentivizing Restrictive Intended Uses

We would like to further expand on our thinking related to use of restrictive intended uses and urge you to craft policy that allows FDA to approve intended uses without needing to list a specific disease or condition. AMP is concerned that FDA has only begun to move toward approving tests where the intended use focuses on the analyte(s) of interest and not the disease or condition. Moreover, the use of whole genome or exome sequencing may be appropriate and recommended for a person’s clinical presentation without prior knowledge of the underlying cause of the disease. It is unclear at best how FDA would be able to handle these types of situations if their proposed language was adopted. AMP urges you to amend text in all places where the legislation requires a test developer to list a disease or condition. As examples, see *Section 587. Definitions (12)(E)* and *Section 587I. Registration and Notification. (b)(2)(K)*.

Rare Disease Exemption

AMP would also like to note the criteria outlined by FDA for the rare disease exemption is also overly restrictive. While we understand that the criteria is based on the humanitarian device exemption, this exemption was developed for devices with intended uses for specific diseases or conditions. Often rare disease testing is performed because the underlying cause of the patient's condition is not known. Thus, the type of testing needed for patients with rare diseases is likely applicable to many more than 8,000 individuals. Instead, AMP proposes that a test should be classified as a test for a rare disease if a test is intended to test an analyte that would assist in diagnostic decision making of a condition that affects fewer than 200,000 Americans.

Precertification

We applaud FDA for acknowledging that conditional approval has been successfully applied to laboratory testing oversight for quite some time. AMP has been generally supportive of conditional approval because we believe, based on the success of the New York State Department of Health Clinical Laboratory Evaluation Program, that laboratories with demonstrated experience with similar technologies and/or methodologies can successfully offer other accurate and precise LDPs. As such, AMP incorporated a conditional approval system into their *CLIA Modernization Proposal*. AMP's system relies on the CLIA accreditation process and also review of a "representative" LDP, to borrow language from FDA.

We encourage consideration of a conditional approval system as you explore options for regulatory oversight. However, AMP has significant concerns with FDA's precertification proposal and seeks clarification on what is proposed. First, it does not make use of the great deal of information that CMS and third parties possess about a laboratory and their record of quality and excellence, nor does it make use of proficiency testing for precertification renewal purposes. Secondly, there is lack of clarity on what tests would be applicable for exemption from premarket review. Under FDA's proposed framework, there are only high and low risk tests. Low risk tests are already exempt from review, however, our interpretation of the FDA language indicates that high risk tests are also ineligible for the premarket review exemption under the precertification system, *Section 587D. (b)(2)*. Thus, the value of the program is unclear as proposed. Lastly, the proposal's use of "eligible person" leaves it unclear as to whether the individual laboratory professional, the laboratory, or the parent organization of the laboratory would be precertified. AMP seeks clarity on this issue to ensure that what is proposed would not give FDA the authority to regulate medical professionals in the laboratory.

Feedback from the Centers for Medicare and Medicaid Services

AMP recognizes that FDA has an important role to play in providing feedback on the new regulatory system outlined in DAIA and we appreciate their thoughtfulness and desire to apply innovative thinking to their regulatory approach. AMP's aim of providing comments is to share our concerns and questions about FDA's technical assessment in order to promote a robust conversation about FDA's approach to regulating LDPs. It is important to note that FDA left several placeholders in their rewrite of the new framework. In addition, input from CMS has not been provided. AMP thinks it is critically important to hear from this agency especially on how FDA's proposal would overlap with many of their activities. AMP reiterates that it is crucial to obtain feedback from all relevant agencies before moving any legislation moves forward.

AMP greatly appreciates your desire to hear from the full range of stakeholders on this topic and your consideration of our comments on FDA's technical assessment. We look forward to future opportunities to participate in any discussions related to the oversight of laboratory testing and hope that you will consider more detailed comments as well. Lastly, we would once again like to volunteer our efforts in helping to reshape the discussion draft to better reflect the impact that LDPs have on our society. If you have any questions or if AMP can be of further assistance, please contact Tara Burke at TBurke@amp.org.

Sincerely,

Kojo S.J. Elenitoba-Johnson, MD
President, Association for Molecular Pathology