



ASSOCIATION FOR MOLECULAR PATHOLOGY

Education. Innovation & Improved Patient Care. Advocacy.

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**Association for Molecular Pathology
Comments on the draft discussion of the
Verifying Accurate Leading-edge IVCT Development Act of 2018**

February 13, 2019

Thank you for the opportunity to provide comments on the draft legislation Verifying Accurate Leading-edge IVCT Development Act of 2018 (VALID Act). The Association for Molecular Pathology (AMP) truly appreciates your continued willingness to engage a broad range of stakeholders and for the time and effort that you have devoted to this important issue.

The Association for Molecular Pathology (AMP) is an international medical and professional association representing over 2,500 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 our goal as an organization to ensure that patients have access to innovative and high quality laboratory testing procedures and to avoid unnecessary costs to the healthcare system. As you continue your work on this draft legislation, AMP welcomes the opportunity to provide you with resources and input from our expert members.

These comments should be taken into consideration along with AMP's general position on the regulation of laboratory developed testing procedures (LDPs) -- we maintain that the Food and Drug Administration (FDA) is not the appropriate agency to regulate LDPs. Our professional members provide medical services. Manufacturing products for sale and providing a medical service are fundamentally different activities and a single regulatory system will never be able to accommodate both LDPs and boxed and shipped in vitro diagnostic (IVD) test kits. Thus, we remain concerned that FDA regulation of LDPs, even as proposed in the draft VALID Act, will drastically hinder the advancement of precision medicine and interfere with the practice of medicine.

If a technical assessment from the Centers for Medicare and Medicaid Services (CMS) has not already been requested, then AMP strongly encourages the co-sponsors move forward with that request. While the draft VALID act was written with the goal of not modifying or duplicating the Clinical Laboratory Improvement Amendments (CLIA), upon review, our members identified numerous areas of duplication between requirements included in the draft VALID Act and current regulations that are set forth in CLIA. FDA jurisdiction over LDPs adds another layer of bureaucracy to laboratory regulation. While it is important to streamline the current regulatory pathway for IVD kits, modernizing the separate CLIA-centric pathway is the most efficient and least costly way to further ensure patients are getting the most appropriate and effective care for their clinical situation. AMP welcomes the opportunity to work with the co-sponsors to modify this legislative draft to reflect our requested changes below and also to help draft the additional legislative text needed to modernize CLIA.

As requested by you, we are providing line by line comments and edits, but this in no way serves as endorsement or other support for the policy proposed in the draft legislation. As such, AMP requests that the co-sponsors consider our opening statement together with our comments below. Our overall goal is to partner with you to facilitate the development of a modern and flexible system that allows professionals to continue providing personalized care to their patients.

Section 1

- For the reasons stated above, AMP is disappointed that the current draft does not include a section on modernizing CLIA. AMP maintains that CMS, via the CLIA program, is the most appropriate agency to regulate LDPs because LDPs are within the practice of medicine¹; however, laboratory medicine has grown and evolved significantly since CLIA was last updated. As outlined in AMP's CLIA modernization proposal², there are key areas that should be updated to promote transparency, quality, and innovation. We also would like to note that the proposed changes included in the draft VALID Act would create numerous requirements that are duplicative with CLIA regulations. We urge the co-sponsors to create more streamlined and efficient but separate approaches for regulating LDPs and boxed and shipped IVD kits.

Section 2

- **Page 3, ss(1)** – AMP requests that the definition of IVCT be edited to remove any reference to “test protocols” and so that the definition only pertains to IVD kits that are intended to be introduced into interstate commerce. When LDPs are designed, validated, and performed, there is never any physical product that is sold and shipped, nor is there any technology distributed for use outside of the laboratory offering the medical service.
- As a result of this change noted above, all references to test protocol should be removed from Sections 1-8 of the draft bill.

Section 3

Sec. 587. Definitions

- **Page 6, (5)(A) and (5)(B)** – AMP urges the cosponsors to remove the phrase “trade name.” AMP has a position statement called “[Reference to Diagnostic Tests in Drug Labels](#),” which we encourage you to review. To promote patient safety and high quality care, AMP believes that diagnostics in drug labels should be described by the biological description of the gene or mutation using standard HUGO nomenclature. Further, AMP believes that tests should only be referenced by brand name in a drug's label as part of a description of relevant clinical studies. Additionally, it is important the labeling language be crafted in a way that does not give a tacit endorsement of the brand name of a diagnostic test even when the drug label refers to the biological description of the gene or mutation. Labeling language should not restrict patient access to appropriate testing.

¹ FDA has consistently asserted that it does not regulate the practice of medicine. This prohibition has never been specifically set forth in the statutory scheme which guides the FDA's action. However, the Practice of Medicine Exception has been inferred from the Congressional intent expressed in the legislative history. In fact, in the Drug Amendments Act of 1962 Congress specifically exempted licensed practitioners who administer, prepare or manufacture drugs or devices "solely for use in the course of their professional practice." (21 U.S. Code § 374 (a) (2) (B)) Additionally, the amendments require that producers of drugs or devices must register with the Secretary of Health and Human Services. (21 U.S. Code § 360(a) (1) & (b)) Again, licensed practitioners who "prescribe or administer drugs or devices and who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in the course of their professional practice" are also exempted from this requirement. (21 U.S. Code § 360(g) (2))

² http://dev.amp.org/AMP/assets/File/advocacy/AMPCLIAModernizationProposalFINAL8_14_15.pdf

- **Page 6, (6)** – In general, AMP is greatly concerned that the draft legislation opens professionals who develop and perform LDPs to product liability claims. Creating the term developer does little to resolve our concern, which is that the draft legislation and the associated FDA regulations with which laboratories would have to comply still would treat healthcare professionals as manufacturers. As an example, the term manufacturer is used within numerous regulations under Quality System Requirements that would apply to LDPs as specified under Sec 587J: 21 CFR 820.30 - Design controls; 21 CFR 820.50 - Purchasing controls; 21 CFR 820.80 - Receiving, in-process, and finished device acceptance; 21 CFR 820.100 - Corrective and preventive action; and, 21 CFR Part 820, Subpart M – Records. Even if the term was removed from regulations, the draft legislation still in practice treats molecular professionals as manufacturers because it stipulates that their professional activities are equivalent to a physical medical product that is within the jurisdiction of FDA. Clinical laboratories and medical professionals are already required to meet laboratory practice standards and are subject to negligence (laboratories) or medical malpractice (professionals) claims. If the term manufacturer were applied to clinical laboratories, in the course of litigation, the laboratories would be required to obtain additional product liability insurance, thus increasing costs of testing. Moreover, it is unlikely that a medical professional’s insurance could extend to product liability.
- **Page 6-7** – AMP does not believe that the definitions of high and low risk apply well to LDPs. 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 that any risk classification system should consider transparency of the test methodology, the resulting impact on the ability for external parties to verify laboratory reported information, and the ultimate impact to the patient.
- **Page 7, (8)(A)** – The meaning of an “undetected inaccurate result” should be clarified.
- **Page 7, (8)(B)** – This suggests that there is a risk class between high and low risks. We strongly recommend that the co-sponsors clearly define what it would mean to be a moderate risk IVCT.
- **Page 8, (11)** – We find the definition of “test group” to be overly restrictive. We 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) or biomarker 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 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. Additionally, 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. 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. In the 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 pre-market review for each relevant specimen type, even if a laboratory or company could bear the cost of the initial FDA review. It is often the case now that LDPs result from laboratories modifying IVDs to meet a clinical need and often, 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.

- **Page 9, (B)** – AMP supports the definition of “valid scientific evidence.”

Sec. 587A. Applicability

- **Page 12, (a)(2)(B)** – AMP appreciates the inclusion of this text and the intention to avoid duplication; however, we find that the requirement to comply with some FDA regulations as outlined in the following sections would prevent the Secretary from being able to prevent duplication between FDA and CLIA. Further, without specific language on modernizing CLIA, implementation of this proposal could result in duplication as well.
 - See Sec. 587J. Quality system requirements, specifically regulations related to design input, design output, design validation, design changes, records, and complaint files.
 - See Sec. 587M. Corrections and Removals, specifically regulations related to records of corrections and removals, nonconforming events, and documentation requirements for corrective actions.
- **Page 12, (a)(3)** -- Molecular professionals are a critical component of the clinical care team. The proposed language 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 as a part of medical care. It would also prevent discussions about testing for other intended uses even in cases in which the information conveyed by the pathologist is neither false nor misleading. The 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.
- **Page 16, (b)** -- LDPs are not “plug & play” test systems, but are assembled from a collection of components that may include FDA-cleared or -approved IVDs, analyte specific reagents, general purpose reagents, and instruments. Currently, the FDA only regulates individual components of an LDP such as reagents and AMP supports continued FDA oversight of only these components. The composition of these components can change as a result of numerous factors, many outside of the control of the laboratory.
- **Page 17, (c)** – AMP thinks that grandfathering all LDPs as proposed within VALID will do little to support the advancement of patient care, particularly because of the restrictive definition of test group and the use of the term on page 25 at subsection (I).

- **Page 22, (g)** -- 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. This is best illustrated with newborn screening performed in all 50 states, which mostly utilizes LDPs to detect rare and ultra-rare metabolic diseases with actionable interventions. With almost 4 million babies born each year in the US, these tests are performed well above the threshold in the draft legislation and would not qualify for the exemption, even though the test is for some of the rarest diseases in the world.
- **Page 24, (h)(2)** – AMP thinks the criteria for the exemption for custom and low-volume tests is too restrictive. In particular, we request that you remove the term “unique pathology or physiological condition.” 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. AMP recommends the following language:
 - “(B) is a custom test developed to meet the needs of a unique set of factors such as technology and platform capabilities, clinical presentation, unknown variants, sample quality, for which no other in vitro clinical test is commercially available in the United States, and is—“
- **Page 24, (i)** – AMP agrees that LDPs that are intended to be used solely for public health surveillance should be exempt from all requirements.
- **Page 25, (l)** –AMP would like to reiterate the importance of changing the definition of test group so that it is less restrictive particularly because of the impact it would have on the ability to modify an LDP. An essential component to the continued advancement of precision medicine is the nimble environment that promotes innovation and allows testing services to be quickly adapted and improved. Thus, AMP thinks that re-review of an LDP that has been modified is only necessary when the performance characteristics change significantly or when the change increases the risk to the test such that it becomes classified in a higher risk classification.
- **Page 25, (l)** -- As [previously discussed](#), clinical laboratories are eager to use FDA-reviewed commercially available test kits that can assist them in patient care, but those kits must serve current scientific understanding and medical practice, fit into the laboratory's overall technology, platform and workflow plans, and be cost-effective. The FDA-cleared MiSeqDx Cystic Fibrosis Clinical Sequencing Assay exemplifies both test limitations and how test modifications are inhibited for an IVD. 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. Thus, AMP believes that reform of regulation of manufactured distributed test kits is needed. We feel the definition of test group would also be overly restrictive for IVD kits and prevent manufacturers from making necessary modifications.

Sec. 587B. Premarket Review

- AMP does not think this section should apply to LDPs.

Sec. 587C. Priority Review

- AMP does not think this section should apply to LDPs.

Sec. 587D. Precertification

- AMP has been generally supportive of conditional approval because we believe, based on the success of the New York State Department of Health (NYSDOH) Clinical Laboratory Evaluation Program (CLEP), 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*. This conditional approval program is similar to NYSDOH CLEP in that it allows a laboratory to begin testing with LDPs when it uses similar technologies or methodologies to other previously reviewed LDPs offered by the laboratory. Also, any conditionally-approved LDP is eventually fully reviewed within a given time.
- The idea of “precertification” at FDA is a new concept, not defined in statute, and a precertification pilot is currently underway for software. On January 7, 2019, FDA outlined its regulatory approach to precertification software; this approach differs dramatically from what is included in the draft legislation. For software, FDA expects to grant precertification to manufacturers that demonstrate “a robust culture of quality and organizational excellence (CQOE) and are committed to monitoring real-world performance.”³ As part of the assessment, FDA will evaluate processes, activities, systems, tools, and culture of an organization – they do not expect to evaluate the final product for exempt software risk categories. However, precertification for IVCT developers outlined in the VALID Act is based on the ability of that developer to provide all the necessary information about a representative IVCT for a specific technology. The two types of precertification programs seem to conflict with each other and because at least some test systems contain software, care should be taken to not conflict the two types of precertification. Thus, AMP believes that it is important to define this term and seeks clarification from FDA to understand clearly what it means to be “precertified by FDA.” Further, the regulatory structure contained within VALID relies completely on the proposed precertification program yet full understanding of the structure, scope, and impact to both IVDs and laboratories remain unknown. AMP recommends that careful consideration be taken to understand impact on such as program and strongly recommend that for LDPs, a CLIA modernization section in VALD include a conditional approval system based on one outlined within AMP’s CLIA Modernization proposal.
- **Page 46, (b)(2)** – Please clarify what it means to be an eligible IVCT and correct drafting errors that lead to confusion.
 - **(b)(2)(A)(i)** – Should the text say, “a component or part of an in vitro clinical test as described under section 201(ss)(1)(F)”?
 - **(b)(2)(A)(ii)** – Should the text say, “a test platform under section 201(ss)(1)(C)”?

³https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/DigitalHealthPreCertProgram/UCM629276.pdf?utm_campaign=Digital%20Health%20Update%3A%20New%20FDA%20Pre-Cert%20Working%20Model%20Now%20Available&utm_medium=email&utm_source=Eloqua

- (b)(2)(A)(iii) – Should the text say, “an article for taking or deriving specimens from the human body under section 201(ss)(1)(D)”?
- (b)(2)(A)(iv) – It is unclear how this software differs from the software described at (b)(2)(A)(i) as currently written. Should the text read, “software under section 201(ss)(1)(E)”?
- **Page 47, (b)(2)(B)** -- Again, AMP thinks it is essential that legislation define this middle risk category for IVCTs considering that high risk IVCTs are not eligible for exemption under the precertification pathway.
- **Page 48, (c)(2)(A)** – The text should make clear that a medical subspecialty does not need to necessarily relate to a disease or condition because it is sometimes more appropriate for a test to provide information about a biomarker regardless of the patient’s specific disease or condition. As you may be aware, FDA recently approved Merck’s pembrolizumab (Keytruda) for the treatment of tumors that express one of two biomarkers regardless of where in the body the tumors are located showing that the government is taking steps towards the adoption of precision medicine where molecular profiles are used to inform medical decisions when appropriate. Additionally, the agency published a draft guidance that would enable a companion diagnostic’s label to reference a class of oncology therapeutic products based on the biomarker’s mechanism of action instead of a specific drug or therapy by name. We urge you to remove language that would deter these advancements and tie FDA to old and outdated ways of thinking about molecular testing.

Sec. 587E. Mitigating Measures

- **Page 57** -- AMP does not support crafting legislation that gives FDA jurisdiction over LDPs. Yet, there continue to be efforts to move forward with an FDA-based system and AMP is disappointed that these proposals, including the draft VALID Act, fail to account for the integral role of the medical professional in the design, validation, and interpretation of an LDP. This role mitigates a great deal of risk to the patient. 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 mitigating measure.

Sec. 587F. Regulatory Pathway Designation

- **Page 59, (a)(1)** -- 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 more limiting sense. The drastic changes allowed by this language do not provide manufacturers and laboratories with the predictable environment that they request. In particular, AMP requests that FDA not be allowed to “revoke any exemption” established by law.

Sec. 587I. Registration and Notification

- **Pages 62- 66** AMP would like clarification on how FDA should be expected to collect information when two separate CLIA facilities within a laboratory system use the same LDP. Similarly, how would the FDA expect to handle/manage split workflows across two CLIA labs? For example, one laboratory site may comprise the wet bench portion of next generation sequencing laboratory procedures, while the bioinformatics, or dry bench, portions are handled at a separate CLIA-certified laboratory.

Sec. 587J. Quality System Requirements

- **Page 67, (a)(3)** – It is highly inappropriate to require laboratories that develop LDPs to comply with Section 587J for the following reasons:
 - First, laboratories already comply with quality system regulations under Subpart M of Part 493 of title 42.
 - Secondly, FDA quality system requirements (QSRs) do not translate well to the processes of a laboratory that develops LDPs.
 - Thirdly, we appreciate that the co-sponsors recognize that not all QSRs should apply to LDPs, however, the requirements listed at Section 587J (b)(2) are still duplicative with CLIA requirements and would create additional layers of bureaucracy that will not translate into improved outcomes for patients. We specifically call your attention to requirements that pertain to design input, design output, design validation, design changes, records, and complaint files.
 - AMP is also concerned that FDA’s QSR regulations would greatly increase costs that, by necessity, will pass into the healthcare system, exacerbating the gap between patients who can afford advanced testing and those who cannot. Patients have reported that charges received for necessary advanced testing are beyond their ability to pay. As example, our members report that they would likely have to hire additional staff to demonstrate compliance with regulations, especially those associated with design controls, design transfer, design history file, and purchasing controls. Regarding design transfer, one member with expertise in this area expected that laboratories would need to institute a completely separate department to employ dozens of medical laboratory scientists and masters-level employees to fulfill this function. Further, AMP members found that the regulations for purchasing controls would shift burden from suppliers to laboratories. We note that there are sometimes issues with reagents obtained from suppliers. For example, suppliers sometimes change reagent composition and laboratories are not always notified. In order to minimize the impact on testing, the current practice of laboratories is to 1) use high-quality suppliers and 2) evaluate reagents using control samples prior to introduction into production. Components that have the potential to impact result quality are monitored using multiple assay parameters. Still, it is important that the co-sponsors also review the requirements placed on suppliers as a means to ensure the reliability of laboratory testing.
 - Moreover, compliance would not be accompanied by benefits to patient care or gains in patient safety. 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 is exceedingly low.
- **Page 67, (a)(3)** – The vast majority of molecular professionals do not have the infrastructure or economic capacity to meet these requirements, and we recommend that LDP developers not be subject to QSRs as CLIA certifies laboratory quality. Thus at minimum, AMP requests that the text be changed so that laboratories must comply with subsection (b) after the “Secretary amends part 820 of title 21 of the Code of Federal Regulations as specified in paragraph (4).”

- **Page 67 (a)(4)** – For the same reasons listed above, AMP requests that the following text be struck:
 - “Until such amendment takes effect, such regulations shall be interpreted to apply to in vitro clinical tests and developers.”

Sec. 587K. Labeling Requirements

- Generally, it is unclear which labeling requirements under Part 809 of title 21 of the Code of Federal Regulations would apply to LDP developers. We understand that LDP developers would have to comply with requirements set forth in section 809.10(b) and (g) of title 21 of the Code of Federal Regulations, but not section 809.10(a) or 809.10(d). It is unclear what requirements set forth in sections 809.10(c), 809.10(e), 809.10(f) would apply. We ask the text be amended to clarify the requirements.
- **Page 71, (c)(1)** -- The LDP involves the use of tools by highly-educated and experienced molecular professionals. LDPs themselves are not physical products, so there is no kit that includes a set of reagents specifically designed and distributed for a specific LDP. It is unclear how LDP developers would comply with reagent labeling requirements listed under 809.10(b) because the molecular professional is not developing the reagents and thus has no control over the reagent’s label. Instead, laboratories should be expected to, and do, keep documentation regarding reagents. As an example, 42 CFR 493.1252 requires that laboratories document criteria for those conditions that are essential for proper storage of reagents.
- **Page 73, (d)(1)** – AMP thinks this alternative requirement is important because it would not be possible for LDPs to have a package insert.
- **Page 74 (e)** – We understand that one argument for FDA oversight of LDPs is that LDPs are not currently eligible for inclusion in the Strategic National Stockpile. However, we would like to note that because LDPs are not physical products, it would be impossible to include them regardless of whether they are regulated by FDA or not. IVD kits would be needed for this purpose. Further, LDPs also play a crucial and unique role in responding to public health emergencies. This was the case during the H1N1 pandemic outbreak in 2009, during which local laboratories in academic settings were able to quickly develop molecular-based tests for their patient population before a test was available at public health laboratories. Additionally, they were able to help with surges in testing to meet their hospital’s needs⁴.

Sec. 587 L. Adverse Event Reporting

- **Page 75, (a)** – AMP is concerned with the application of this section to LDPs for the following reasons:
 - CLIA already requires laboratories to report to ordering physicians errors in test results. The current regulations are stringent and require that each laboratory report patient test result errors to the authorized person ordering the test, maintain a record of those errors, ensure that all complaints and problems reported to the laboratory are documented, conduct investigations of complaints when appropriate, and issue a correct report. CMS-approved accrediting organizations must notify CMS within 10 days of any deficiency identified in an accredited or CLIA-exempt laboratory if the deficiency poses an immediate jeopardy to the patient or hazard to the general public.

⁴ [https://jmd.amjpathol.org/article/S1525-1578\(10\)60253-X/pdf](https://jmd.amjpathol.org/article/S1525-1578(10)60253-X/pdf)

- AMP’s CLIA modernization proposal builds upon the adverse event reporting requirements within CLIA and updates them to mandate ready mechanisms for reporting and promote transparency.
 - AMP believes compliance with these additional requirements is likely to consume significant administrative resources.
 - Yet, compliance would not be accompanied by benefits to patient care or gains in patient safety. 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 is exceedingly low.
 - Laboratory health professionals typically are not informed of ongoing patient care and would not be aware or have easy access to this type of information.
- **Page 75, (b)(1)** – Subparagraph (A) and (C) contradict each other. An adverse event may be associated with either the “test” or laboratory operations and it takes time for a laboratory to determine the cause of the adverse event. However, subparagraph (A) requires that the error to be reported to the FDA if it *may* have caused or contributed to a death or serious injury. Essentially all adverse events will have to be reported to FDA even if the laboratory eventually determines that it could be directly attributed to what FDA considers a laboratory error. Additionally, it will be difficult to parse out what FDA expects should be reported to the agency because LDPs are a laboratory procedure. Therefore, the inclusion of subparagraph (C) will do little to prevent duplication with CLIA. We request that the co-sponsors explore other ways to ensure that FDA and CMS requirements do not overlap.
 - **Page 76, (b)(3)** – Five calendar days is not enough time to gather the necessary information that should be included in a report. Laboratories will need to take time to determine the cause of the event and whether it was due to operations or test design/development. This will involve reviewing reports, reagents/supplies, and possible failures in development, validation, or verification of the test or in the transfer of the test the laboratory.
 - Generally, the legislation should also specify whether laboratories will be responsible for gathering information not in the laboratory, which can include patient records.

Sec. 587M. Corrections and Removals

- **Page 77, (a)(1)** -- We find the requirements in part 806 of title 21 of the Code of Federal Regulations to be highly duplicative with CLIA requirements and would like to specifically draw your attention to regulations related to records of corrections and removals, nonconforming events, and documentation requirements for corrective actions.
- Under 21 CFR 806.1, the regulations note that actions taken to improve the performance or quality of a device but that do not reduce a risk to health posed by the device or remedy a violation of the act caused by the device are exempt from reporting. However, it will be difficult to parse out normal quality improvement steps from those that need to be reported. This will need to be clarified.
- The regulations refer to registering with FDA. Some hospitals may not allow clinical laboratories to “register” with FDA because registration as a manufacturer could change the institution’s tax status. It may be necessary to consider an alternative way to “list” with FDA.

- The regulations use terminology that does not translate well to LDPs. Thus at a minimum, AMP requests that the text be changed so that laboratories must comply with Sec. 587M only after the Secretary amends part 806 of title 21 of the Code of Federal Regulations as specified in paragraph (1).

Sec. 587P. Accredited Persons

- **Page 82, (c)(B)** – AMP is concerned that the number of people not engaged in the development of LDPs and IVDs who also have the necessary experience to review applications and perform inspections will be insufficient and not fill the need that will exist when they become responsible for regulating the thousands of LDPs performed in the U.S.
- **Page 83, (D)(1)(2)** – VALID states in this section that compensation of an accredited person who reviews an application for precertification or premarket approval and compensation of an accredited person who is conducting inspection shall be determined by an agreement between the accredited person and the person who engages those services. AMP is concerned about a trickle-down effect of such agreements on laboratories, particularly those that perform a significant number of LDPs. Creation of a free market economy for these services may make review unattainable for laboratories and result in reduced patient access to LDPs.

Sec. 587R. Investigational Use

- AMP does not think this section should apply to LDPs.

Sec. 587U. Comprehensive Test Information System

- **Page 95** -- AMP believes that CMS is the most appropriate agency to house and maintain a comprehensive database for the purpose of providing transparency to the public about LDPs.

Sec. 587V. Preemption

- **Page 96, (a)** – Medicare administrative contractors should be prohibited from regulating laboratory test performance, therefore, AMP requests that the text be edited so that it reads: “No State, tribal, local government (or political subdivision thereof), or government contractor may establish or continue in effect any requirement related to the development, manufacture, labeling, distribution, sale, or use of an in vitro clinical test that is different from, or in addition to, the requirements of this subchapter.”

Section 8

With PAMA continuing to decrease the reimbursement rate for molecular tests and recent national coverage policies further threatening access to NGS-based tests for oncology, laboratories are finding it more and more challenging to operate and offer innovative tests for their patients. This coupled with the significant increase to the CLIA user fees this year, has the potential to reduce a laboratory’s ability to operate and/or they may drop tests from their menu reducing patient access. Moreover, such stresses have the potential to greatly increase costs that, by necessity, will pass into the healthcare system, exacerbating the gap between patients who can afford advanced testing and those who cannot. Patients have reported that charges received for necessary advanced testing are beyond their ability to pay. Hence, any creation of a new user fee will need to be balanced with the ongoing economic challenges laboratories face and not be so high as to be prohibitive.

Thank you again for working with AMP on this difficult and complex issue. We look forward to continued discussions on this topic. We continue our commitment 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. If you have any questions or if AMP can be of further assistance, please contact Tara Burke at TBurke@amp.org.

Sincerely,

Victoria M. Pratt, PhD, FACMG
President, Association for Molecular Pathology