



**ASSOCIATION FOR MOLECULAR PATHOLOGY**  
*Education. Innovation & Improved Patient Care. Advocacy.*  
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Energy and Commerce Committee  
U.S. House of Representatives  
Delivered electronically to [cures@mail.house.gov](mailto:cures@mail.house.gov)

Dear Members of the Energy and Commerce Committee:

Thank you for the opportunity to submit these comments in response to your request for feedback on “A Modernized Framework for Innovative Diagnostic Tests.” The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who 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 (IVD) industry. AMP applauds the Energy and Commerce Committee on the 21<sup>st</sup> Century Cures Initiative and their efforts to take a holistic look at processes through which new cures are developed, and the positive and negative impacts of regulatory policy. In addition to these comments, AMP submitted comments in June in response to the “21<sup>st</sup> Century Cures: A Call to Action” which can be accessed here: [http://amp.org/publications\\_resources/documents/AMPComments21stCenturyCures-ACalltoAction.pdf](http://amp.org/publications_resources/documents/AMPComments21stCenturyCures-ACalltoAction.pdf).

Laboratory developed testing services represent a vital area of medical practice and has historically been central to the advancement of public health. These services are usually the first offering of new, clinically valid tests to patient care, often at the request of and in consultation with oncologists and other clinicians. They bridge gaps in our diagnostic and prognostic needs, and allow treating physicians to tailor treatments for their patients. They are tools in the hands of board-certified professionals with extensive clinical training such as specialist physicians and geneticists, who apply current medical knowledge to optimize patient care. An essential component to the continued advancement of personalized, or precision medicine, is the nimble environment that promotes innovation and allows testing services to be quickly adapted and improved.

The Food and Drug Administration’s draft guidance titled, “Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)” will effectively reformulate existing medical device regulations and impose substantially new requirements on clinical laboratories, hospitals, physicians, and other health care providers. Yet, there is no documented evidence that laboratory developed testing services pose a widespread threat to the public health. Prior to implementing any new regulatory schemes for diagnostic procedures, AMP strongly urges that parties responsible for updating and implementing regulations pursue an approach that actively engages stakeholders and properly evaluates the impacts of any proposed change to the current regulations. For that reason, AMP has signed a letter to the FDA Commissioner requesting that the agency withdraw the draft guidance document and pursue notice and comment rulemaking. AMP appreciates the opportunity to provide this information today and looks forward to providing additional feedback as the Committee continues its work and considers legislative approaches to oversight of diagnostic procedures.

AMP believes that Food and Drug Administration (FDA or Agency) oversight of laboratory testing services will be impossible in a practical sense unless any regulatory framework designs unique oversight requirements that acknowledge and accommodate the irreplaceable and professional nature of these services. In its white paper, “Optimizing FDA’s Regulatory Oversight of Next Generation Sequencing Diagnostic Tests—Preliminary Discussion Paper,” released to inform its February 20, 2015 public workshop, the FDA states that technologies capable of detecting genetic variation other than next generation sequencing (NGS), *i.e.*, polymerase chain reaction (PCR) and single nucleotide polymorphism (SNP) arrays are “generally designed to capture predefined data points that are known in advance of testing, and therefore are more suited to regulation under traditional approaches. However, even these technologies may benefit from a different approach for capturing data related to clinical performance.” Indeed, the clinical relevance of any variant identified by any technology, be it next-generation or other sequencing, cytogenomic arrays or other platforms stand to benefit from novel metrics for assessing test performance. As the FDA proposed with NGS, assessing the clinical performance, or validity, of a test often resides within a well-curated third-party database and other externally-generated evidence. Analytical performance, or validity, of any test that is developed by any lab, could be demonstrated by means of methodologic quality-based standards that laboratories could meet. In addition, standardized reference materials, can be used to develop an assay and demonstrate its analytical performance. While it is not necessary to know what variant, or set of variants, one wishes to interrogate prior to running and successfully interpreting an NGS test, quite often the molecular pathology professional does know and utilizes NGS as the sequencing platform to obtain this information.

It is clear that the FDA believes that non-traditional regulatory pathways are essential to foster innovation, allow the public to have access to newly developed tests, and ensure that those tests are accurate, reliable, and clinically relevant. As with NGS, applying traditional regulations designed for manufacturers of distributed tests to LDPs threatens to significantly hinder patient access to the significant benefits these tests offer.

As it stands, the FDA’s proposed framework outlined in the LDT draft guidance will drastically reduce the ability of laboratories to offer new laboratory testing services because of the potentially short duration of time in which the tests could be offered before introduction of a different (and potentially outdated or inferior) test that is approved or cleared by the FDA. With the reduction of various services will be a concomitant reduction of physicians, geneticists and infectious disease specialists with the training and expertise to offer these services. The Agency’s proposed regulation will markedly dampen the ground-breaking innovations developed by these professionals as part of their laboratory clinical practice—innovation that is the genesis of commercial tests kits. At the same time that the FDA’s regulation will erect additional impediments to medical advancement in the U.S., it will contribute to soaring costs, all with no guarantee of improved patient outcomes. For the reasons listed above, using medical device regulations and the FDA to regulate laboratory developed testing services is inappropriate.

To the extent that the Committee and others are interested in developing new incentives to accelerate the commercialization of mass-produced testing kits, we strongly urge reform to the FDA’s current regulation of mass-produced testing kits. We further support Clinical Laboratory Improvement Amendments (CLIA) modernization to enhance the oversight of laboratories where molecular pathology professionals’ services are offered as opposed to the expansion of the FDA commercial kit regulation framework to physician services. AMP encourages the Committee to advance legislation that:

- Directs the FDA to rescind the Agency’s proposed guidance to regulate laboratory developed testing services and clarifies that the Agency is prohibited from regulating professionals or the clinical procedures and analyses they perform within the scope of their education, clinical training, professional board certifications, applicable licensure, and/or clinical organization’s credentialing;
- Modernizes CLIA to, among other things, strengthen the role and responsibility of third party accreditors;

- Reforms current FDA regulation of in vitro diagnostic (IVD) commercial diagnostic kits distributed by manufacturers in order to address the extensive and well-documented concerns of manufacturers that current FDA regulation of commercial diagnostics kits is costly, overreaching, and so slow that commercial kits become obsolete before they reach market;
- Confers limited authority on a third party (though it need not be the FDA) to apply premarket review regulations to testing services where incorrect results could cause significant morbidity or mortality to patients and the test is performed by a single laboratory, there is no proficiency test, and the methodology is **not transparent** (as in the case of tests that use black box complex algorithms to produce results).

The issues being considered by the Committee have significant consequences regarding whether patients and their physicians will be able to obtain the testing services they need. AMP hopes that the comments provided to the Committee help ensure that minimally burdensome regulations will be put into place so that patients continue to have access to medically necessary laboratory testing services in a way that also allows for future advancements in testing and patient care. Please find AMP's response to your specific questions below and if AMP may be of any additional assistance, please contact its Executive Director, Mary Williams, at [mwilliams@amp.org](mailto:mwilliams@amp.org).

Sincerely,

Janina Longtine, MD  
AMP President

- 1. Multiple stakeholders have expressed the urgent need to have clear and logical lines separating the practice of medicine, the actual conduct of a diagnostic test and the development and manufacturing of diagnostic tests. How should these lines be defined and what are the key criteria separating each of these activities?**

Unlike conventional, distributed, manufactured IVD test kits, laboratory developed tests are a medical service throughout the design, performance and interpretation of the results. As professional services, they have additional opportunities to promote patient safety due to the professional judgment used at every stage. To clearly distinguish the professional services that molecular pathology professionals provide using their education and experience, AMP refers to these services as laboratory developed procedures (LDPs). AMP defines an LDP as "a professional service that encompasses and integrates the design, development, validation, verification, and quality systems used in laboratory testing and interpretative reporting in the context of clinical care."<sup>i</sup> The term LDP better represents the nature of complex laboratory testing, which is very much a medical service, and emphasizes the ongoing involvement of appropriately trained and qualified professionals in every aspect of the procedure, in addition to the provided interpretation. The term also acknowledges the inherent connectedness and interdependence amongst the components of the test, the results, and the role of the health care professionals.

Regardless of whether the laboratory performing a service for a patient resides in the same building or health system as that patient, the defining measure of quality is the direct involvement of an appropriately qualified professional in every aspect of design, performance, and interpretation of a testing service. Molecular pathology professionals are qualified to offer these services because they have completed extensive post-graduate education and clinical training, taken board-certification examinations administered by the American Board of Pathology or the American Board of Medical Genetics and Genomics under the umbrella of the Accreditation Council for Graduate Medical Education, or other recognized professional board. They continue to maintain their certification as required and they insure their professional practice activities with medical malpractice insurance.

As the Committee considers legislative language on diagnostics, AMP strongly encourages you to refer to and define these services as LDPs.

AMP believes that by placing restrictions on a molecular pathology professional's ability to develop an LDP, freely select the appropriate use of an LDP, interpret results of an LDP, and have candid conversations with treating physicians hinder the practice of medicine and impedes innovation. The FDA's proposed regulations could consider communication between molecular pathologists and treating physicians to be promoting off-label use. Medical professionals are not manufacturers. It is in the best interest of patient care to have regulations that permit professionals to focus on patient care rather than on increasing burdensome and inter-agency duplicative regulation.

Laboratories, their personnel, and the processes to detect biological compounds of interest are already regulated under a multi-pronged framework consisting of CLIA, state laws, and accreditation by authorities, such as the College of American Pathologists. All of these together provide oversight of the laboratories, the personnel and the services they provide, yet also allows them the flexibility to develop and validate laboratory tests in requisite timeframe. AMP is a vigorous advocate for the principle that only high-quality, clinically and analytically valid diagnostic tests should be used in clinical practice. Laboratory developed procedures should be, and are currently, reviewed for analytical validity – the accuracy and reliability of a test. Assessing the clinical performance (clinical validity) of a test, *i.e.*, how well the test identifies the presence, absence or risk of a specific disease, can be implied from the current CLIA regulations. Modernizing CLIA regulations to address issues related to clinical validity and reassuring the public of the accuracy and reliability of laboratory tests is the most appropriate mechanism of enhancing regulation while preserving the scope of professional practice.

Molecular pathology professionals practicing within their scope will utilize reagents (products that are subject to FDA regulation) and instruments (which may or may not be FDA regulated) when conducting testing, but the laboratory testing services are the technical expertise and clinical judgment of the professional who develops and validates the test performed under conditions that are already subject to oversight under CLIA. The molecular pathology professional makes a clinical determination as to what products to utilize, what patient specimen is appropriate, and what instruments to use in order to develop and perform the testing services. The molecular pathology professional that develops, validates, and performs the testing procedures is knowledgeable of each component part and each step and procedures involved with the test. These professional services cannot be packaged and shipped to multiple laboratories.

With LDPs, the professional development, monitoring and application to clinical care are inseparable and inextricably linked. The artificial distinction between 'manufacture' and use for an LDP permeates the FDA's guidance, and actually forms the basis for it. However, in reality because of the close interaction of the professional, who provides oversight and responsibility for design, development, validation, continual monitoring and updating, interpretation, reporting and communicating results and their implications that are attendant to LDPs, these functions are so intertwined that they cannot logically be separated – and they constitute medical practice. LDPs are within the scope of a board-certified molecular pathology professional practice and these professionals have a legal responsibility for them. In contrast, with commercial diagnostic kits the design, development and manufacturing are physically and distinctly separate from the laboratory operations, including sign-out of tests (meaning the reporting, record review, and other components of communication with treating physician colleagues). It is not appropriate to regulate commercial diagnostic products and LDPs the same. Molecular pathology professionals are medical service providers and not manufacturers.

- 2. In FDA's draft regulatory framework, the agency describes the extent to which it proposes to regulate LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act (FFDCA). It is relatively clear with respect to distributed test kits what constitutes a "device," but less clear when considering a test developed and performed in a laboratory. What should comprise the "device" subject to regulation by the FDA?**

Molecular pathology professionals consult with ordering physicians in determining the appropriate services to perform, given an individual patient's clinical presentation. They interpret the results of the test service in the context of other medical information. The procedures they develop, perform, continuously monitor, and continually improve distinguish LDPs from medical devices, such as artificial joints or in vitro diagnostic test kits which are currently regulated by the FDA and distributed to a wide range of users in the U.S. and around the world. Processes used in the practice of medicine are not devices.

Laboratory developed testing services are not "plug & play" test systems, but are assembled from a collection of components that may include FDA-cleared or -approved IVDs, ASRs, 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. The entire process is a procedure performed by a highly trained molecular pathology professional, who validates and verifies every step and use of reagents and instruments; however, it is impractical and unnecessary for a lab to refile with the FDA for modifications or adjustments to these components.

Current medical device regulations were designed for massively produced *boxed and shipped* laboratory kits that are distributed interstate to customers who are independent from the company that manufactured them. IVDs are intended to be distributed and used in accordance to their FDA-cleared or -approved package insert and labeling. Medical device regulations have been put in place, in part, because IVDs are used by laboratory staff other than the experts that designed and developed the tests; therefore, providing labeling information that includes detailed instructions and descriptions for these distributed kits is warranted.

However, laboratories should not be expected to meet the same device manufacturing requirements for LDPs that are designed and used within the same facility. Unlike kits, LDPs involve appropriately qualified professionals in every stage of the LDP's design, performance, and interpretation. An LDP is as much the outcome of the professionals who develop and maintain it, and the laboratory where it resides, as are the components chosen by those professionals to constitute the actual test procedure. The procedure is performed where it is designed.

- 3. FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?**

AMP generally agrees with the American Medical Association and other major stakeholders that risks posed by clinical tests are different from therapeutic medical devices. The current FDA medical device classification, therefore, is not appropriate for clinical tests. A new risk-classification for clinical testing, developed with significant stakeholder input, that more flexibly balances the relative risks posed by clinical tests with the potential benefit of the information that they provide would be most appropriate. Given the risk associated with rapid multiplication of potential erroneous testing that accompanies commercial manufactured diagnostic kits, the FDA establishes rigid rules for test performance to substitute for professional judgment that is not appropriate or desirable for molecular pathology professional services. Most of the ways the FDA's current regulations mitigate risk are unworkable in clinical laboratories (e.g. cGMP, labeling, pre-market review and

post-market surveillance). Alternatively, the *entire* process in developing, validating, and performing an LDP (the test, the personnel, controls, interpretation) governed by the medical professional primarily mitigates the risk of an LDP. Therefore, AMP believes that FDA oversight is not warranted for the vast majority of LDPs. Specifically, AMP believes that only the highest risk tests should be reviewed by a third party and AMP defines these tests as:

LDPs that are used to predict risk or risk of progression of a disease or patient eligibility for a specific therapy to treat a disease that is associated with significant morbidity or mortality *if* the test is performed in a single laboratory *and* uses methodologies that involve proprietary algorithms or computations such that the test results cannot be tied to the methods used and/or do not allow for inter-laboratory comparisons to be performed, proficiency testing, or other confirmation analyses.

The threat of harm for LDPs that meet these criteria warrants independent verification, though it need not be by the FDA.

The current FDA classification system is for manufactured devices and is not applicable for procedures performed by appropriately qualified medical professionals. Although, if an FDA-like classification system was applied, all remaining LDPs should be by default class I instead of class III. Additionally, any high risk LDPs (as defined above) that have formal or alternative third-party proficiency testing should also be class I. As stated above, LDPs are a medical professional service, and as such, have additional opportunities to ensure patient safety due to the direct involvement of an appropriately qualified professional, further supporting their designation as class I. Examples of processes currently in place to mitigate risk include:

- Training programs (medical students, residents, and fellows) that essentially means the entire process (teaching the validation, technical and interpretive aspects of the assay) is repeatedly "reviewed."
- Board-certified professionals periodically have their credentials peer-reviewed for continued employment. This includes certain lab-specific data (turn-around time, error-rate, etc.).
- There is a process of internal 'peer-review' for the functioning of tests as the results are presented in conjunction with all other findings. If a test is felt to be producing unsatisfactory or unexpected results, the molecular pathology professional can review, repeat, adjust and otherwise modify an LDP.

When taking into account the potential of a misinterpreted result to cause harm to a patient, one must keep in mind the number of "checks and balances" that accompany LDPs. Every laboratory performing clinical testing is CLIA-certified which assures laboratory performance standards and tests' accuracy and reliability. Additionally, those performing high-complexity tests must, under CLIA, undergo regular proficiency testing. Even further, almost every clinical laboratory chooses to obtain accreditation by a third-party, such as the College of American Pathologists, which holds laboratories to rigorous quality standards and regular inspections.

Once the laboratory test has been run, it is reviewed and signed by the laboratory director – a physician or other board-certified clinical professional who is legally responsible for the result. The ordering physician then receives that result and, often in consultation with the laboratory director, uses his or her expertise to subsequently manage patients. This application of professional expertise – by highly trained experts in laboratory medicine and patient care – is essential in mitigating the risk of harm that could come to a patient through a misinterpreted result. This professional responsibility is present now, without FDA oversight of LDPs, and will continue irrespective of additional oversight.

The professional responsibility of a laboratory director is to ensure that a test run in his or her laboratory produces accurate and reliable results. This often means evaluating the methodology and components of tests

and optimizing performance in the laboratory. However, it is impossible to apply these activities to many commercial kits that use “black-box” methodology, *i.e.*, those that use complex, non-transparent, or proprietary algorithms to determine a result. While the results of many tests impact patient care and could potentially cause harm to patients if misinterpreted, those that do not lend themselves to evaluation by the laboratory professional and the patient’s treating physician are most concerning to AMP and are the type of test that belongs in the high-risk category. To the extent that many companion diagnostic tests are run using now-routine sequencing or variant identification methodology that is transparent and easily evaluated, and return results that are essentially “yes or no” answers, AMP believes it is inappropriate for the FDA to assign all companion diagnostic tests to the high-risk category. Aside from the absence of established risk criteria applied to each individual test’s methodology as a basis for their placement in the high-risk category, the FDA appears to be casting aside the risk mitigation that occurs with a board-certified professional’s (both ordering and laboratory) oversight and expertise in running the test and subsequently managing the patient.

**4. The current pre-market review standards that apply to in vitro diagnostics use the same terminology of safety and effectiveness that apply to all medical devices. Should the medical device concepts of safety and effectiveness apply to test kits and LDTs?**

The safety and effectiveness standards that the FDA applies to drugs and medical devices are not appropriate to LDPs, rather, these procedures should have demonstrated accuracy and precision. Any new regulatory framework for LDPs, including one established through legislation, should require that LDPs demonstrate accuracy and precision. Currently, laboratories accomplish this through rigorous analytical validation processes that include ascertaining or designing to certain accuracy and precision; accreditation inspectors’ review of data; proficiency testing; and more. These processes serve as a continuous evaluation of quality. Clinical validity (*i.e.* the clinical performance of an LDP) is initially established in the scientific literature, and is further established during validation processes that establish an LDP’s sensitivity and specificity, as well as (which are of particular interest to a clinician and patient) positive and negative predictive values, which indicate how well the test identifies whether the patient truly has the disease. Therefore, it would be unnecessary and inappropriate to subject LDPs to the medical device concepts of safety and effectiveness, when terms specific to laboratory diagnostic tests such as accuracy and precision better address the quality and reliability of an LDP. This is especially evident in examples where the FDA has approved a test when evidence to support its role in improving health outcomes is lacking. For example, *PCA3* testing is an FDA-approved test used for deciding when repeat prostate biopsies may be needed in the diagnosis of prostate cancer; however there is little evidence to support that it is useful for this purpose and additionally, data suggesting that it increases the occurrence of disease-free survival is low.<sup>ii</sup>

In addition, AMP does not support application of current medical device safety and effectiveness concepts to laboratory testing services because clinical procedures and professional expertise are not devices. Furthermore, the FDA’s application of statutory provisions intended for actual medical devices, drugs, and biologicals to manufactured commercial diagnostic kits is statutorily compulsory, but ill-suited to the consideration of validity (analytical and clinical) and risk/benefit relevant to diagnostics. Instead the Committee should invite additional discussion on clinical and analytical validity as well as relevant risk/benefit models under both CLIA for laboratories where these medical services are performed and FFDCa for commercial diagnostic kits.

**5. Are there areas where the balance between pre-market review versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?**

AMP recommends that all LDPs be subject to rigorous post-market review under modernized CLIA regulations that strengthen the role and responsibility of third party accreditors and expand access to proficiency testing. In

addition, AMP also recommends that third party reviews enhance the transparency of test validation summary information and that CLIA collect information on adverse events.

Additionally, the federal government should invest resources in developing standardized reference materials so that performance standards can be met during the development of LDPs. These are critical materials that enable laboratories to design their LDPs to exemplify performance standards facilitating both accuracy and precision. Additionally, these materials may also be of use to commercial IVD test kit manufacturers. Further, in the development of LDPs, laboratories' rigorous validation process includes sample exchanges which further enhance the LDP's demonstration of accuracy and reliability.

Third party pre-market review should only be required for the highest risk tests and this review process must be clear, concise, consistent and greatly expedited. Specifically, third party reviewers should provide an initial response to an application within 30 days and the entire review completed within 90 days.

**6. A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?**

An essential component to the continued advancement of personalized, or precision medicine, is the nimble environment that promotes innovation and allows testing services to be quickly adapted and improved. 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. 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 (see answer #3). In this case, subsequent submissions should only be required for those where modifications significantly change the clinical performance (clinical validity) or reduce analytical validity. The process for reviewing modifications should be likewise expedited as the initial review.

Laboratories should not be required to file tests that are merely modifications to FDA-approved or -cleared IVDs that are validated by appropriately qualified professionals such as specimen type. Much of this modification activity is only necessary due to the barriers imposed by the FDA, and partly outlined by AMP in 2010,<sup>iii</sup> which have disincentivized companies from improving or updating their commercial kits or expanding their intended use to additional necessary specimen types.

Manufacturers have laid out a compelling case that the FDA's current approach lacks an appropriate balance between pre-market review versus post-market controls. Reforming the FDA's authority over commercial kits in both areas would level the respective positions of commercial kits and professional testing services while increasing options and protecting the medical professional's clinical decision-making. In short, only clinically meaningful performance modification should trigger a supplemental submission requirement for commercial kits. The CLIA model of oversight has served as the engine of innovation in this space and rapid application of validated clinical discovery to patient care; therefore, any change of oversight of LDPs should involve enhancements to CLIA and institute clear prohibitions against the FDA regulation of medical services.

**7. We have heard a lot about the practice of medicine and its relationship with medical product "labeling." What should comprise "labeling" for diagnostic tests? Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices? What about for laboratories that develop, perform, and improve these tests? Should there be regulatory oversight of the information that is provided to the individual patient or health care provider or is that the practice of medicine?**

The FDA has publicly stated that the importance of communication between laboratories and ordering physicians is an important factor in mitigating risk<sup>iv</sup>, and AMP agrees. Laboratories should provide information at the point of ordering to include description, limitations, summary of data elements that demonstrate analytical and clinical validity, selected bibliography, and laboratory phone number so the ordering physician can contact the appropriate medical professional in the laboratory and easily have access to relevant information that should be used in patient care decision making. In addition, the regulatory body that oversees LDPs should require health systems to have a secure document transfer system in place for scanned/electronic medical record information and for requisitions to include the name, email address, phone number of the ordering physician, a clinical coordinator or relevant physician extender that can provide additional information needed by the laboratory professional.

Medical professionals should be able to freely discuss information in the scope of their practice regarding anything associated with the LDP, *e.g.*, biomarker, analyte, technology, or associations to a medical condition under discussion. Nothing in the regulation should at all constrain information sharing between the laboratory professional and clinicians including scientific literature, reprints, study data, etc.

Even to the extent that the FDA proposes to define LDPs as something other than what they are - professional expertise and procedures - the Agency's application of these provisions to professionals could create liability for off-label use and "promotion." Currently, when physicians determine that a "product" labeled for a specific intended purpose has an alternative beneficial clinical use, physicians are permitted to use for an "off-label" purpose and are permitted to discuss with other physicians. Although there remains an ongoing legal dispute between the FDA and drug, biological, and device manufacturers, in general manufacturers are prohibited from promoting off-label uses and face significant sanctions if and when the Agency can establish that the manufacturer has "misbranded" the product.

Molecular pathology professionals in contrast are well qualified and are permitted to tell patients and treating physicians when a commercial diagnostic kit has a clinical benefit for another purpose. This is the very definition of medicine, *i.e.*, a physician using his or her expertise to appropriately diagnose and treat a patient who may require care that is not "one-size fits all" and must not be constrained. Competent and quality medical care rests on physicians' discretion and responsibility to treat patients in a manner that meets each patient's individual needs. When physicians determine that a test "labeled" for a specified use is appropriate for another use, a physician is permitted to employ off-label uses and permitted to discuss off-label uses with other physicians and patients. In contrast, manufacturers are prohibited from off-label promotion.

Validated modifications to an FDA-approved or -cleared test performed by appropriately qualified molecular pathology professionals should be considered off-label use rather than a form of "remanufacturing." Likewise, off-label promotion in the context of LDPs should be permitted to occur freely since such a prohibition of discussing testing options with patients and treating physicians including off-label uses would prevent molecular pathology professionals from meeting both ethical and legal obligations. Furthermore, off-label uses of devices, drugs, and biologicals lie at the heart of innovation. In the course of providing care to patients, molecular pathology professionals are able to identify emerging previously unknown patterns, symptoms, and outcomes that were not otherwise contemplated when a method, approach to medical care, procedure, device, drug, or biological was initially devised for patient care.

Even assuming the FDA had the capacity to timely process submissions, physicians and laboratories do not have the resources needed to prepare a submission for FDA clearance or approval—which is costly and time-consuming even for large corporations often singularly focused on a very small sliver of the universe of tests patients need daily.<sup>v</sup> If off-label uses (also called clinical practice enhancements) required FDA clearance or approval once one manufacturer commercialized a product, all versions of the test including superior versions would most likely cease given the cost and resource barriers. Even if an application could be submitted, timely

processing is already a concern as discussed below when the Agency is only regulating commercial diagnostic kits.

**8. The Section 1143 guidance documents raise important questions about the relationship between the FDCA and the Clinical Laboratory Improvement Amendments (CLIA), administered by the Centers for Medicare & Medicaid Services (CMS). Is there overlap between the requirements of the guidance documents and CLIA? For instance, how do FDA's quality systems regulations compare with CLIA quality systems requirements? Are there areas of duplication where there would be efficiencies to having either CLIA or FDA regulate, rather than both?**

AMP is very concerned with what will certainly be significant overlap between FDA and CLIA regulations. The FDA's draft guidance does not provide sufficient detail to ascertain where CLIA requirements end and where the FDA requirements begin. The FDA's draft guidance is very vague and does not specify how the FDA plans to eliminate or minimize this duplication of requirements. AMP presumes there are many elements of FDA QSRs that are inappropriate for clinical laboratories because they apply to boxed and shipped tests. Moreover, duplicative processes or requirements from two federal agencies that provide oversight of quality systems of LDPs raises serious probability for regulatory conflict, confusion and un-necessary costs to laboratories, patients, and the agencies. AMP strongly urges the Committee to consider the compelling need to avoid duplicative and confusing regulation and oversight by two federal agencies, a number of states, and accreditation bodies with deeming authority. There could be substantial overlap in the regulatory requirements under FDA medical device regulation and the applicable regulations under CLIA concerning quality system requirements, design controls, document controls, purchasing controls, production and process controls, acceptance activities, nonconforming products, corrective and preventative actions, and records.

We urge the Committee to, at a minimum, direct the FDA to identify with CMS the respective requirements and direct the FDA to defer to CLIA requirements where there is overlap. Stakeholders must have an opportunity to comment on proposal before it is finalized through notice and comment processes. AMP questions whether the Agency has the bandwidth to expand oversight to laboratory developed testing services when it seems unable to produce a guidance document that elucidates sufficient detail regarding the regulations to which clinical laboratories and molecular pathology professionals would be subject.

In addition, the FDA is requesting that they are notified of which LDTs each laboratory offers even though CLIA already collects this information. It also appears that the FDA will restrict off-label promotion of LDPs, however CLIA has clinical consultation requirements in practice of laboratory medicine. AMP has requested that the FDA complete a thorough analysis of all existing oversight of clinical laboratories and identify areas of overlap, duplication, redundancy, and conflict. We also encourage the Committee to press the FDA for this information. Additionally, even with the "increased" oversight of the engagement of the FDA, "splitting" the regulation of LDPs between test and practice, even with the duplicity, could result in diversion and gaps. AMP has asked that the information from FDA's assessments be made available publicly.

**9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g. Ebola)?**

AMP believes that in most instances, molecular-based LDPs are either for a rare disease and/or for an unmet need, and premarket review should not be required. Specifically, AMP believes that the FDA's proposed exemptions for LDPs used for rare diseases and unmet needs fail to adequately capture the full range of these procedures. The FDA proposes to exempt tests performed less than 4000 times annually in the U.S. However, this does not truly reflect LDPs for rare diseases, but rather, identifies rarely performed procedures. Instead, the definition of LDPs for rare diseases should be based on disease prevalence. Laboratory developed testing

services are often the only option for those with suspected rare diseases. The commercial market for such tests is nearly non-existent, so laboratory-developed tests are a vital tool for patients and their physicians. As currently written, the FDA's proposed exemption for rare diseases is inadequate in ensuring the continued availability of laboratory developed testing services. For example, in one of the most stunning public health successes in history, every newborn in this country undergoes testing for dozens of conditions, which, if not identified within days of birth, can result in serious morbidity and mortality. Many of the conditions being tested are rare diseases, but that does not diminish the public health imperative for them to be identified and diagnosed in patients. However, since the number of newborn screening tests that are performed far exceeds the FDA's definition of rare disease (fewer than 4,000 persons tested each year), each one of the dozens of newborn screening tests may be subject to burdensome requirements that could endanger their availability. Under the FDA's draft guidance, public health labs already burdened with scarce resources will need to devote funds to support applications to the FDA. In addition, because these tests often constitute a small volume of testing for most laboratories, FDA oversight would likely result in laboratories dropping the tests completely, leaving patients and physicians without an option for screening and diagnosis.

It should also be noted that while cancer is not considered a 'rare' or 'orphan' disease, a number of subtypes of cancer occur less than 1% of the time. For example, while lung adenocarcinomas have a rather high incidence, some targetable subtypes are rare and these subtypes should be considered rare and eligible for any rare disease exemption. For these reasons, AMP proposes that a test should be classified as a rare disease LDP if a test is intended to test a variant that would assist in diagnostic decision making of a condition that affects fewer than 200,000 Americans.

Similar to the lack of commercial availability for tests for rare diseases, many thousands of laboratory developed tests exist simply because commercially-developed kits do not exist, *i.e.*, they fulfill an unmet need. These laboratory developed testing services are for a broad range of conditions, and constitute the standard of care. For example, clinical guidelines recommend testing all newly-diagnosed colon cancers for Lynch syndrome, a hereditary colorectal cancer syndrome. Lynch syndrome testing includes assays for mismatch repair variants and microsatellite instability. This type of testing has been available as an LDP service for more than 10 years and has been continually improved-upon as new research data emerges (*e.g.*, including *BRAF* as part of the Lynch syndrome testing protocol). There are no FDA-approved tests for Lynch syndrome nor for microsatellite instability. Yet, the FDA's proposed exemptions for this "unmet needs" test category ends as soon as a commercially-developed kit becomes available. When this happens, every laboratory that has developed a Lynch syndrome testing protocol would have to abandon its LDP in favor of the commercially-available kit even though it may be outdated and the laboratory loses the ability to continually advance and improve its testing. The alternative of submitting the LDP to the FDA, likely as a pre-market approval application, is financially and administratively unfeasible for most hospital laboratories. This would drive up costs, and would freeze further innovation and improvements to Lynch syndrome testing, leaving patients without access to cutting-edge care.

The nature of public health outbreaks demands that health systems respond rapidly and respond to the clinical care crisis of individuals and their physicians. Molecular pathology professionals are able to fulfill this need by developing tests that accurately identify pathogens far more quickly than they would be able to do if FDA approval or clearance were required. For example, in April 2009 an unknown respiratory outbreak emerged in the U.S. and Mexico. During the first week of the outbreak, several dozen laboratories had already developed molecular assays that could identify the outbreak as being caused by influenza, and could distinguish the A and B strains. Several of the laboratories were further able to identify the influenza A H1N1 virus from other influenza A H1 viruses. Most results from these tests were available within 24 hours, speeding treatment of patients and facilitating the work of public health officials.<sup>vi</sup> FDA approval requirements would have severely crippled this response. The FDA has the capability to issue Emergency Use Authorization, but they limit the application and do not necessarily approve the best test in the expert opinion of molecular pathology professionals and therefore do not adequately address the problem.

LDPs are usually the first offering of new, clinically valid tests to patient care, often at the request of and in consultation with other clinicians. Therefore, LDPs are by nature developed in order to fulfill an unmet need whether it means developing a whole new (and often times improved) test to diagnose a condition or altering a service to better suit a patient's need. Again, there should be an exemption from premarket review for LDPs for unmet to avoid delays in innovation and to promote state of the art patient care.

We strongly urge the Committee to build on and modernize the existing CLIA regulatory framework consistent with our recommendations because the current CLIA framework has a demonstrated track record of:

- providing the necessary flexibilities to ensure patient access to testing services for rare diseases and conditions;
- supporting customized testing services based on particularized patient need; and,
- enhancing the capabilities of the country's safety net of highly skilled professionals and laboratories that can provide essential surge capacity and frontline access when there are outbreaks of infectious diseases and biothreats.

**10. Any new regulatory system will create transition challenges. How should existing products be handled? Should all current diagnostic tests be "grandfathered" into the marketplace? What transition process should be used for new product introductions?**

AMP supports modernizing the CLIA program for LDPs. However, for those highest risk LDPs requiring premarket review by a third party (see answer to question #3), there should be a transition period for laboratories to meet those pre-submission requirements. Before any additional tests are deemed high risk and/or subject to third party review, a public advisory panel should be convened to assist with the classification of such tests and an appropriate timeframe for implementation should be given. Laboratories need to be able to clearly anticipate which tests will be subject to which requirements so they can logistically plan and to avoid stifling innovation. Risk classification should be finalized before any new framework is implemented. Any congressional action to modify the existing oversight and regulations should grandfather in currently existing LDPs, with the possible exception of highest risk tests as defined in #3 above.

In addition, Congress must consider that Medicare's reduction in coverage and reimbursement in the context of testing services will coincide with increased oversight and regulatory obligations. We strongly urge the Committee to consider the interplay between these dynamics for patient access to existing testing services as well as future innovation.

**11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?**

There is an urgent and compelling need to reform the current FDA regulation and oversight of mass-produced IVD test kits to create a more predictable and consistent regulatory pathway for industry. However, there is an equally important need to address the current Medicare coverage and reimbursement policies that is adversely impacting the ability of patients to obtain medical care and exerting pressure on the molecular pathology professionals who have led the innovation to accelerate 21<sup>st</sup> Century Cures and related testing. As the Committee considers policy to create an appropriate regulatory framework for both LDPs and IVDs, AMP asks that you also explore solutions to the ongoing coverage and reimbursement challenges facing laboratories.

There are also concerns that U.S. patients are being unnecessarily delayed access to products that are subject to medical device regulations. In a study prepared by Stanford University researchers and supported by the

Medical Device Manufacturers Association (MDMA), the National Venture Capital Association (NVCA), AdvaMed, and others, the authors report that the average total cost for FDA-related activities is \$24 million to bring a low-to moderate-risk 510(k) product to clearance and \$75 million to bring a higher-risk PMA product to approval.<sup>5</sup> This study also reports that respondents' medical devices were available to U.S. patients an average of *two years later* than patients in other countries. In some cases, this lag reached nearly six years. Manufacturers face commercialization challenges largely because of the burdensome, opaque, and lengthy FDA clearance and approval process.

The ability and capacity of the FDA to approve or clear commercial diagnostic kits has been paltry when compared with the breadth and range of testing services offered to patients under CLIA—with high rates of accuracy and rapid application of new and validated clinical knowledge. There are FDA-approved commercial diagnostic tests for only six molecular biomarkers with direct implications for targeted oncology therapies (*KRAS*, *EGFR*, *CKIT*, *HER2*, *BRAF*, and *ALK*). Moreover, the clinical indications are very narrow and the only approved specimen type is formalin-fixed, paraffin-embedded tissue, ignoring other essential specimens such as those taken during minimally invasive procedures. The Committee should carefully consider that comprehensive reform of testing services should not expand the reach of an FDA regulatory model that has created barriers to innovation, limited patient access to testing improvements, failed to provide any viable pathway for rare diseases and conditions, and utilizes a top-down, bureaucratic approach to outbreaks and potential biothreats. In addition to CLIA modernization, there is an urgent need to address and streamline the FDA's regulation of manufacturers of mass-produced commercial kits consistent with AMP's recommendations provided to the Agency in June 2010.<sup>3</sup>

In summary, AMP identified three barriers:

1. The paucity of standard reference materials for all areas of molecular diagnostics, *i.e.*, genetic, oncology, and infectious disease testing, inhibits the production of appropriate control materials and methods.
2. The difficulty of obtaining rare specimens for studies presents a barrier to submission of applications for the approval of new indications for currently approved tests.
3. Test manufacturers perceive that there is an inconsistent and unclear regulatory pathway for their submissions. Manufacturers have faced uncertainty and/or inconsistency in the review of device submissions, in enforcement discretion, in device classification [510(k), 510(k) de novo, PMA, ASR, etc.], in requirements for acceptable analytical and clinical validations, and in requirements changing from the time of pre-IDE meetings through mid-trial. IVD test manufacturers must then function within this uncertain regulatory environment and are limited in their efforts to anticipate regulatory requirements and appropriately amend business models.

To address these barriers, AMP recommended:

- The FDA should ensure that policies and requirements are consistently applied, and that the scientific evidence and rationale for decisions are communicated effectively to diagnostic test manufacturers.
- Communication from the FDA to diagnostic test manufacturers should be as clear and as comprehensive as possible at the outset of the submission process. This will help manufacturers better plan their resources and time. It will also assuage undue angst that the regulatory bar will change during the process.
- The FDA should improve communication between branches so that consistent requirements are developed and applied and demonstrations of clinical utility in one branch are recognized by the other branches.
- The FDA should involve the expert opinion of medical professional associations regarding clinical utility.

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<sup>i</sup> Ferreira-Gonzalez et al. (2014). Revisiting Oversight and Regulation of Molecular-Based Laboratory-Developed Tests. *The Journal of Molecular Diagnostics*: 16, 3-6.

<sup>ii</sup> O'Leary, T.J. 2014. Regulating Laboratory-Developed Tests. *The Journal of Molecular Diagnostics*: 16, 595-598.

<sup>iii</sup> AMP comments to FDA CDRH Council on Medical Device Innovation: Barriers to Market for Molecular Diagnostic Tests. [http://www.amp.org/Position%20Statements/AMPComments\\_FDAMedicalDeviceWorkshop\\_062410\\_final.pdf](http://www.amp.org/Position%20Statements/AMPComments_FDAMedicalDeviceWorkshop_062410_final.pdf)

<sup>iv</sup> FDA Webinar: Framework for Regulatory Oversight of LDTs Draft Guidance, October 23, 2014. <http://www.fda.gov/downloads/Training/CDRHLearn/UCM421213.pdf>

<sup>v</sup> Makower et al. (2010). FDA Impact on U.S. Medical Technology Innovation.

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<sup>vi</sup> Comments by Jan A. Nowak, MD, PhD on behalf of AMP to the CLIAC September 2009.

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