

January 5, 2015

The Honorable Fred Upton  
Chairman  
House Energy & Commerce Committee  
2183 Rayburn House Office Building  
Washington, DC 20515

The Honorable Frank Pallone, Jr.  
Ranking Member  
House Energy & Commerce Committee  
237 Cannon House Office Building  
Washington, DC 20515

The Honorable Diana DeGette  
2368 Rayburn House Office Building  
Washington, DC 20515

Dear Chairman Upton, Ranking Member Pallone, and Representative DeGette:

The American Congress of Obstetricians and Gynecologists (ACOG), a national medical organization representing over 57,000 members who provide health care for women, thanks you for the opportunity to provide feedback regarding the regulation of laboratory developed tests (LDTs). ACOG acknowledges that both patients and physicians can benefit from timely federal guidance and procedures for LDTs. LDTs have evolved significantly since the 1976 Medical Device Act and continue to evolve with the ever-changing health care field. We support an oversight process that protects patients while also continuing to encourage innovation and progress in health care. The oversight process must be efficient, timely, transparent, and responsive.

As the number of medical conditions in pregnant and non-pregnant women that have, or are suspected to have, a genetic contribution continues to grow and new genetic risks are discovered, additional tests are continually developed to meet patients' needs.<sup>i</sup> With this expanding knowledge, there is also an increasing number of LDTs developed specifically for reproductive disorders, pregnancy, cancer, and carrier screening. This abundance of new tests is influencing treatment options and prevention strategies. ACOG understands that the role of the Food and Drug Administration (FDA) at this time is to address how a test performs and is evaluated, but that alone is not indicative of clinical utility. However, genetic tests for many of these diseases have specific limitations and frequently require careful interpretation. Challenges that can arise include the need to determine the residual risk of being a carrier when the screening does not identify a particular mutation and the need to assess the risk of developing a particular disease despite a negative genetic test result.<sup>ii</sup>

---

<sup>i</sup> American College of Obstetricians and Gynecologists. *Guidelines for Women's Health Care: A Resource Manual*, Fourth Edition. 2014.

<sup>ii</sup> Personalized Genomic Testing for Disease Risk. Committee Opinion No. 527, American College of Obstetricians and Gynecologists. Reaffirmed 2014.

The lack of objective outcomes data for commercial LDTs hampers clinical decision making and jeopardizes patient safety. Ideally, clinicians should be able to offer screening tests with high detection rates and low false-positive rates that allow patients to consider appropriate and available diagnostic options. Regardless of the screening test patients are offered, they need information about the detection rates and false-positive rates, advantages, disadvantages, and limitations. Patient acceptance of LDT screening tests would also include information about the risks and benefits of any additional diagnostic procedures that may be needed, so that patients can make informed decisions.<sup>iii</sup>

New regulations will provide important and needed protections for patients, but at the same time may create new burdens that result in increased costs and limit test availability. It will be important to have a balanced approach in implementing new regulatory guidelines to maximize patient protections and minimize cost and burden. Possible negative impacts of an overly burdensome oversight process include halting innovation, increasing medical costs, eroding patient and physician confidence in the process, and inaccurate diagnoses.

Many of these new laboratory developed tests are used in both obstetric and gynecologic practice. There are increasingly less invasive and more accurate ways to screen pregnant women for fetal birth defects and genetic disorders and to provide the option of diagnostic testing. Obstetric care providers should be knowledgeable about the general screening choices available to patients and either provide that screening themselves or have established referral sources for doing so. It is the obstetrician's responsibility to educate the patient and make her aware of the available options.<sup>iv</sup> Lack of oversight of commercial tests such as cell-free fetal DNA and expanded carrier screening may lead to results that are confusing for both physicians and patients. Some tests, such as maternal serum screening tools, have FDA-approved components that are not specifically FDA-approved for maternal serum screening. Despite the limitations discussed above, these LDTs are integral in women's health care. Additionally, LDTs are used by clinicians for genotyping for cancer susceptibility and human papillomavirus (HPV) screening. As primary HPV testing becomes more common as a method of cervical cancer screening, it is increasingly important that tests are clinically validated.

Innovation can and has improved women's health as evidenced by the following LDTs:

- Beta human chorionic gonadotropin ( $\beta$ -hCG) assessment is part of the work-up of premenopausal women with pelvic masses;
- Alpha-fetoprotein (AFP) serum screening alone can be used to screen for spina bifida and open fetal defects. When combined with other serum analytes, it is also possible to detect Down syndrome (trisomy 21) or Edwards syndrome (trisomy 18);
- Acetylcholinesterase in Amniotic Fluid (AChE-AF) evaluation to diagnose open neural tube defects;

---

<sup>iii</sup> Ibid.

<sup>iv</sup> American Academy of Pediatrics and the American College of Obstetricians and Gynecologists. *Guidelines for Perinatal Care*, Seventh Edition. 2012.

- Lamellar body count evaluates the amount of fetal pulmonary surfactant markers in amniotic fluid to detect fetal lung maturity; and
- Non-invasive prenatal testing of cell-free fetal DNA in maternal plasma to screen for various genetic disorders in pregnancy.

We encourage a balanced and thoughtful approach that protects the health of patients but does not inhibit progress by burdensome regulations and oversight. Should you have any questions, please do not hesitate to contact Rachel Gandell, Senior Manager of Federal Affairs, at 202-863-2534 or [rgandell@acog.org](mailto:rgandell@acog.org). Thank you for your consideration.

Sincerely,

A black rectangular redaction box covering the signature of Hal C. Lawrence, III, MD, FACOG.

Hal C. Lawrence, III, MD, FACOG  
Executive Vice President and CEO



## **AdvaMedDx's Comments on 21<sup>st</sup> Cures-Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests**

AdvaMedDx appreciates the extensive efforts and outreach by Chairman Upton, Representative DeGette, and the Energy and Commerce Committee (or "Committee"). The diagnostics industry is a cornerstone of the modern health care system, providing vital information at every stage from screening to diagnosis to selection of treatment. Rapid advances are being made that are paving the way for more personalized, targeted patient care. At the same time, there have been rapid changes proliferating in the complexity, risk, and marketing of laboratory developed tests (or "LDTs") and the regulatory status quo has been universally recognized as insufficient. The current two-tier regulatory system that differentiates between LDTs and traditional manufacturer developed tests solely on the basis of the type of developer, without regard to patient risk, is fundamentally unsustainable and must be modernized to support the public health and promote innovation of new safe and effective diagnostics.

Our member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies in the United States and abroad. Our membership includes manufacturers engaged in the development of an array of critical technologies supporting the advancement of public health in a variety of health care settings, including laboratories, hospitals, doctor's offices, clinics, and the home.

Maintaining two very different oversight mechanisms for tests that are the same from the perspective of patient safety is bad public policy, provides an opportunity to use tests in clinical settings without sufficient clinical data, and stifles investment in high quality products that can stand up to FDA review. It is imperative that the Food and Drug Administration (FDA or Agency) adopt a risk based regulatory approach for all diagnostics, regardless of where a test is developed. We commend the Committee for its focus on ways to support patient care and robust product development while ensuring that well recognized gaps in oversight are addressed. We believe these considerations should be central to discussion during the current open public stakeholder comment period. Imposition of a regulatory system for tests (i.e., LDTs) can be expected to come with some disruption, but we believe FDA can balance both patient safety and continued and future innovation through appropriate risk based oversight. Patients deserve no less.

AdvaMedDx appreciates the opportunity to provide feedback on this important topic of a modernized diagnostics regulatory framework. We welcome further dialogue on the questions posed in this request for feedback (December 2014) and exploration of ways to support new diagnostic product development. FDA has made great strides in improving the regulatory process for diagnostics, and additional efforts to improve flexibility and support efficient, timely review to aid all IVD innovators, whether LDT or traditional developers, can and should accompany current efforts to implement a risk based framework for LDTs.



### **1) LDTs are a Subset of IVDs, Not Services— Distinct from Practice of Medicine**

A test is a test and presents the same risk for patients regardless of whether it is developed by a manufacturer or a laboratory. Potential harms to patients whose tests return incorrect results include unnecessary treatments with their accompanying costs and side effects and treatment delay or failure to obtain appropriate treatment, all of which lead to worse outcomes for those patients.

FDA has regulatory authority over LDTs as it does with all diagnostic tests (otherwise referred to as “*in vitro* diagnostics” or “IVDs”). Like other IVDs, LDTs are a subset of devices under the Food Drug and Cosmetic Act (“FDCA” or “Act”) and are subject to regulatory oversight by FDA. FDA has the authority to regulate all diagnostics, whether made by manufacturers or clinical laboratories. Tests present the same risk/benefit profile for patients no matter where a test is made.

We note that new terminology for LDTs, e.g., laboratory developed “service” or “procedure,” does not change their status under the FDCA. LDTs are medical devices, not a service. Under the Act, medical devices include any article comprised of “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae.” All LDTs meet this definition as collections of “reagents, instruments, and systems” into an article for the same intended use. The only distinction between IVDs and LDTs is this collection of reagents, instruments, and systems occurs at a laboratory rather than a traditional manufacturing facility. This does not affect FDA authority of the article, which is irrespective of where it is made. Furthermore, assembly of 2 or more medical devices creates a new medical device. Developers may not circumvent regulatory oversight when they are manufacturing medical devices for purposes of the Act.

Physicians utilize IVDs in the care of their patients, but the IVDs themselves are not the practice of medicine. The results of the tests are used in the practice of medicine. For example, an x-ray machine is a device regulated by FDA. Reading and interpretation of an x-ray is the practice of medicine. Physicians are free to use their expertise and judgment in the use of the test results for the care of their patients. The argument that laboratory developed tests are services or the practice of medicine has been presented at different times and has been considered and rejected by both FDA and the Centers for Medicare and Medicaid Services (CMS).

### **2) LDTs, Like other Diagnostics Tests, are Medical Devices Regulated by FDA**

Per our discussion in response 1, a test is a test and presents the same risk for patients regardless of whether it is developed by a manufacturer or a laboratory. Potential harms to patients whose tests return incorrect results include unnecessary treatments with their accompanying costs and side effects and treatment delay or failure to obtain appropriate treatment, all of which lead to worse outcomes for those patients.

FDA has regulatory authority over all diagnostic tests (or IVDs). IVDs are devices that are used in laboratory analysis of human samples and include commercial test products and instruments used in testing, among other things. Medical devices include any article comprised of “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae.” Diagnostics



tests are produced by manufacturers for distribution to laboratories and other users, by laboratories for distribution to additional laboratories, or produced and used in a single laboratory for use only within that laboratory (the latter two are treated as LDTs for purposes of FDA's proposed framework). IVDs may be used in a variety of settings, including a clinical laboratory, a physician's office, or in the home. It is important to note that the test is separate and distinct from the laboratory personnel's following of good laboratory practices governing testing, which must be implemented by all laboratories that use LDTs and/or FDA approved or cleared tests.

The 1976 Medical Device Amendments require FDA to review the safety and effectiveness of all medical devices, specifically including diagnostic tests. As a category of diagnostics, LDTs are subject to the provisions of the FDCA and FDA regulation that require assurance of safety and effectiveness for diagnostics.

To date, however, FDA has exercised enforcement discretion for LDTs, meaning that FDA has not enforced applicable regulations with respect to these tests and has not been reviewing LDTs to assure safety and effectiveness. LDTs also have not been subject to numerous other aspects of FDA regulation that are designed to protect patients. When FDA began regulating medical devices, LDTs generally were relatively simple, low-risk tests and FDA exercised enforcement discretion by not regulating them. Now, LDTs encompass even the most advanced molecular diagnostics, such as higher risk tests that are essential for safe and effective use of cancer therapeutics or a critical determinant in the treatment of serious, life-threatening diseases. In order to assure access to safe and effective LDTs, the FDA has announced its plans to exercise its existing enforcement discretion authority over LDTs through implementation of a risk based regulatory framework.

### **3) *Implementing FDA Risk Based Approach for All Diagnostics***

AdvaMedDx has long called for FDA to modernize its regulation by ensuring risk based regulation of all diagnostics, regardless of where they are made. As it does for all medical devices, FDA regulates diagnostic tests according to risk. Risk posed to a patient is irrespective of where a test is developed. The classification process is well described in the FDCA and its codified regulations. For diagnostics, risk assessment considers harm that could occur if test results are incorrect. The majority of diagnostics are low- and/or moderate-risk devices based on the nature of the claims made for them (i.e., intended use), and therefore, respectively Class I and II devices. Therefore, the majority of diagnostics does not require premarket approval (PMA) and are subject to the premarket notification (or 510(k)) process. We also note that newer regulatory tools such as the *de novo* 510(k) process have allowed for improved, appropriate risk based review of tests in addition to the traditional 510(k) process.

Consistent with AdvaMedDx's approach, FDA proposes a risk based, phased-in approach aimed to support both innovation and the public health. In its proposed framework, FDA has indicated that it will take a risk based, phased-in approach that appropriately focuses the Agency's resources on tests that pose the highest risk to patients. Further, FDA plans to phase in this oversight over a minimum of nine years following finalization of the LDT guidance. In addition to focus on tests that pose higher risk to patients, we note that FDA should strive to expedite patient access to lower risk tests—regardless of where made—by more efficient use of premarket review process, including additional exemptions for well-established tests.



We note that FDA includes helpful examples of risk classification factors in its proposed LDT framework guidance (e.g., Is the device intended for use in high-risk disease/conditions or patient populations? Is the device used for screening or diagnosis? What is the nature of the clinical decision that will be made based on the test result? Does the physician/pathologist have other information about the patient to assist in making a clinical decision? Are there alternative diagnostic and treatment options available to the patient?).

Higher risk tests generally comprise tests where a false result could lead to incorrect and harmful clinical management, an unnecessary invasive procedure, or failure to follow up a serious condition. Examples include tests for cancer diagnosis, tests that directly or very strongly influence management of serious disease, tests for serious or fatal communicable diseases and most companion diagnostics. The underlying factor for determining higher risk tests is the nature of the claims made for them (i.e., intended use). These tests are distinguished from tests where there are multiple findings used to direct clinical management and where each finding has a specific weight in disease management. They are also distinguished from most tests used to monitor already detected and diagnosed disease and genetic tests where the phenotype is already known and is now being confirmed genetically. These tests are also distinct from low-risk, well-established tests such as cholesterol, iron, and nicotine as well as urine and blood collection kits.

Apart from considerations of risk classification, AdvaMedDx has long reiterated that efforts must be undertaken to assure that tests should be cleared or approved through an approach where the data submission requirements are commensurate with the level of risk of the test. With respect to specific application of risk based oversight for all diagnostics, FDA can and should consider:

- 1) Clinical use of a test (risk associated with how the test is used in the treatment of patients)—e.g., seriousness or prevalence of the condition, prevalence of condition, reversibility of intervention, or standalone use (not supplementary to other clinical information);
- 2) Novelty of analyte (the substance that is undergoing analysis or is being measured);
- 3) Novelty of technology (or test platform);
- 4) Experience or training of the person performing the test; and
- 5) Factors that reduce or mitigate risk—e.g., scientific information, literature, general and/or special controls.

The first four considerations are risk elements. Data that mitigates risk should be considered as available for all four categories and may be different (e.g., literature for 1 and 2, experience of FDA for 3, human factors studies/design elements for 4).

The last consideration is of particular note as FDA specifically recognized in its draft guidance that literature may be considered to support clinical validity. We strongly support FDA embracing this acceptable source of valid scientific information to promote investment and innovation for diagnostics as part of an overall efficient, risk based approach to regulation. Any and all factors that reduce or mitigate risk, including already existing sources of information (e.g., studies in peer-reviewed journals, outside of U.S. data), should be considered in the regulatory review process. Also, FDA must ensure its statutory duty is met to apply the “least burdensome concept” by appropriate reviewer training to require only the evidence necessary to evaluate submissions.



#### **4) *Ensuring Safe and Effective Diagnostics Under Flexible, Risk Based Approach***

FDA should oversee the safety and effectiveness of all diagnostics, including LDTs. The degree of regulation needed to ensure the safety or effectiveness should be determined by the risk devices present to patients. Tests present the same risk/benefit profile for patients no matter where a test is made.

With respect to demonstrating safety and effectiveness, the main elements in FDA's review of diagnostics are analytical and clinical validity. This is specific to diagnostic tests with regard to analytical and clinical performance under the FDA review process. Analytical validity refers to the accuracy of a test in detecting the specific characteristics that it was designed to detect – for example, the presence or absence of a particular gene or genetic change. This is often measured by sensitivity, specificity, detection, precision, and repeatability. Sensitivity refers to how often the test is positive when the target is present, and specificity refers to how often the test is negative when a target is not present. Clinical validity refers to how well the target being analyzed is related to the presence, absence or risk of a specific disease or disorder. This is often measured by sensitivity and specificity. Sensitivity refers to how often the test is positive when the disorder is present, and specificity is how often the test is negative when the disorder is not present. Assurance of both analytical and clinical validity is essential to patient safety. By way of illustration, a test can be very accurate but not clinically valid and present significant potential of harm to patients.

As previously referenced, all efforts must be undertaken to assure that tests are cleared or approved through an approach where the data submission requirements are commensurate with the level of risk of the test to support reasonable assurance of safety and effectiveness. What is sufficient for purposes of a diagnostics submission, for example, should consider risk associated with diagnostics (e.g., clinical use of the test), novelty of analyte, novelty of technology, experience or training of the person performing the test, and any and all factors that reduce or mitigate risk, including already existing sources of information (e.g., studies in peer-reviewed journals, outside of U.S. data). A least burdensome approach must be ensured for diagnostics review to appropriately align evidence requirements with risk associated with the diagnostic test. FDA must ensure reviewer training and apply its "least burdensome concept" to require only the evidence necessary to evaluate all IVD submissions and avoid inflexible, excessive or redundant requirements.

#### **5) *Striking Improved Premarket and Postmarket Balance To Support Diagnostics***

Implementation of a transitional approach for emerging diagnostics is specified in the current user fee agreement. Presently, discussion has been productive and industry looks forward to implementation of a transitional approach as part of the FDA's arsenal of innovative programs to support new diagnostics innovation in the U.S. Diagnostics, including molecular diagnostics, represent in many ways the future of healthcare. They are key to personalized care. They assist in rapid and precise diagnosis, in targeting existing treatments, and in pointing the way to the development of new treatments. Improved premarket/postmarket balance will go far to support timely access to emerging diagnostics and the transitional approach described in the user fee agreement is an important step toward spurring development and availability of these new diagnostic technologies. While such a program is currently intended for traditional IVD developers, this could provide a helpful pathway for interested and qualified LDT developers. The intent of this initiative is to optimize the delivery of new and innovative IVDs for



patients, better harness the latest science, and encourage the development of emerging technologies by sponsors who commit to conduct agreed upon postmarket data collection for their tests.

**6) *Assessing Modifications as Critical Part of the Regulatory Process***

Regulatory requirements should not depend on where a test is developed. Tests present the same risks to patients, irrespective of developer. Changes to tests could significantly affect safety or effectiveness and therefore require a new submission. FDA has provided guidance (K-97) on the decision making process to determine when a change to a Class II medical device requires a new 510(k) submission. Guidance is also provided for when a PMA supplement is required for a Class III device. When submissions for a change are required, these changes must be cleared or approved by FDA prior to product access. Quality systems processes play an important role in deciding whether a new submission is required. This importantly underscores that innovators must develop and implement a quality system that addresses appropriate practices through the lifecycle of a device from development through the postmarket phase, including how to verify, document, and implement change. FDA seeks to address this quality systems gap in LDT oversight through its risk based framework to equally assure the ongoing safety and effectiveness of LDTs and other IVD tests. The FDA Quality System Regulation's (QSR) requirements provide a solid basis for assuring that device modifications are appropriately evaluated via risk management prior to marketing and that the methods and results of evaluation are well documented. In this way, ongoing timely innovation and public health are supported throughout the product lifecycle.

**7) *Providing Appropriate Information in Diagnostics Labeling***

As previously referenced, a two-tiered regulatory system is bad public policy, fails to promote innovation in safe and effective diagnostics, and is not in the best interests of the public health. However, a risk based regulatory framework can accommodate differing labeling needs for LDT developers and traditional developers. In the case of an LDT, FDA requirements related to labeling remain important. All the detailed labeling requirements outlined in 21 CFR § 809.10 may not be necessary, however, for tests that are manufactured for use solely in-house, where the developer and testing site are the same. More tailored specific protocol language for that site could provide sufficiently understandable instructions to the laboratory employee as the test would only be available at that laboratory while assuring that performance and other relevant information about LDTs is still made available to the public. This flexibility would likely be appropriate while ensuring robust premarket/postmarket oversight that addresses key recognized public health gaps for LDTs and ensures availability of accurate, truthful information about available tests.

**8) *CMS Oversight of Laboratories is Distinct and Not a Substitute for FDA Oversight of Diagnostic Tests***

Laboratories are regulated by CMS under CLIA – the Clinical Laboratory Improvement Amendments of 1988. CMS itself has acknowledged the clear differences between CLIA oversight of laboratories and FDA oversight of diagnostic tests, noting FDA's unique role, scope, and qualification to assure the safety and effectiveness of tests. CLIA regulations focus on laboratory practices, including testing procedures, certification, and personnel. As CMS has explicitly stated, CLIA does not regulate the safety and effectiveness of tests and is not a substitute for FDA oversight. Critical features of FDA oversight are not



covered under the CLIA program, which regulates good laboratory practices and is required for all laboratories performing tests, including both FDA approved/cleared tests and LDTs. Furthermore, CMS does not have the expertise or resources to oversee LDTs in the same manner as FDA. Unlike FDA oversight of diagnostics, CLIA:

- Does not regulate the safety and effectiveness of diagnostic tests;
- Does not require premarket review of tests;
- Does not require demonstration of clinical validity (whether the test is meaningful for clinical decision making);
- Does not require systematic adverse event reporting;
- Does not have a process for corrections or recalls.

Under FDA's proposed framework to address gaps and ensure transparency on the scope and use of LDTs, LDT developers will also need to provide information to the public on available LDTs and associated facilities. This is an important and critical step. Up to this point, this information has only been available for diagnostic tests that have listed their facilities or received clearance or approval from FDA.

Beyond critical oversight of the safety and effectiveness of tests, FDA's LDTs framework would require that, among other things, all LDT developers comply with medical device adverse event reporting requirements. Adverse event reporting enables necessary corrective action and helps to prevent injury and death by alerting the public when potentially hazardous devices are discovered. Analyzing adverse event reporting also enables detection of unanticipated events and user errors, monitoring and classifying of recalls, updating labeling information, and developing educational outreach. Using adverse event report data, FDA can detect problems previously unknown as well as problems with similar devices or device categories.

For years, stakeholders have recognized the inadequacy of current oversight of LDTs and called for FDA to enforce existing regulations that apply equally to LDTs as they do to all diagnostics. FDA and CMS are not alone in their recognition of gaps in the regulation of LDTs. In a landmark report by the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, FDA is called upon to "address all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or laboratory developed test)" in order to help close the gaps in oversight related to clinical validity and assure the appropriate use of laboratory tests. SACGHS cited various gaps related to oversight of laboratory testing that can lead to harms. Writing to the White House in 2012, 24 patient advocacy organizations called for FDA to publish draft guidance on LDT regulation. As one letter from numerous organizations stated, "[t]he promise that advanced diagnostics hold for patients is tremendous, but, at the same time, the increasingly pivotal role of these diagnostics in patient care makes it imperative that their safety and effectiveness is assured by the FDA prior to use." Various stakeholders from patient and consumer groups to healthcare professional societies support FDA action on LDTs and implementation of a risk based framework.

Despite these widely recognized gaps, we do expect specific discussion on how to best implement quality system requirements in clinical laboratories and who and how quality system inspections might be conducted for clinical laboratories developing LDTs. FDA and CMS via CLIA have different roles and



regulatory goals. FDA regulation addresses the safety and effectiveness of the diagnostic tests themselves and the quality of the design and manufacture of tests. CLIA regulates the quality of the clinical laboratory. We note there may be opportunities, however, to implement a quality system for LDTs that leverages CMS current oversight of laboratories. We understand that FDA plans to implement QSR in an incremental, phased approach and there will be further discussion on how to best move forward. In a positive development, we note that new and helpful resources are now available from the Clinical and Laboratory Standards Institute, in addition to FDA existing resources, to help laboratories working to implement a quality system for LDTs that best leverages existing laboratory practices and complies with FDA quality systems regulation. However, we note that implementation of a quality system for LDTs to support safety and effectiveness through the continuous product lifecycle from test development through the postmarket phase is essential and not currently in place for LDTs under CLIA.

#### **9) *Spurring Access to Specialized Diagnostic Test Categories, Particularly Rare Disease***

We strongly concur with clinical laboratories that all efforts should be made to assure patient access to specialized test categories (i.e., rare diseases and/or rare usage). As with all diagnostics, FDA should continue to leverage existing accelerated pathways and seek to continuously improve the regulatory process for diagnostics. While we will provide more detailed comments to the FDA draft LDT guidance docket, we note that FDA has proposed several categories of LDTs for exemption from premarket review, including low-risk tests, rare disease testing, traditional LDTs, and unmet needs LDTs. These categories are explicitly outlined by FDA in its draft guidance proposal and cover a wide scope of products that would be exempt from premarket review while assuring key premarket and postmarket controls are in place for these products. AdvaMedDx supports FDA's intent in continuing to exercise enforcement discretion in specific circumstances in which LDTs play a meaningful and needed role in patient care, and risks to patients are minimized or appropriately balanced against patient needs even in the absence of FDA premarket review. Similarly, we support discussion of other mechanisms to support all diagnostic innovation, regardless of where the test is made.

We draw attention by the Committee to a significant policy problem in need of attention. FDA's application of the rare disease pathway, Humanitarian Use Device (HDE), has been a significant obstacle for the development of diagnostic devices for rare diseases and must be improved to serve as a meaningful pathway for diagnostic developers for rare disease. Under the FDCA, an HDE is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the U.S. per year. To obtain approval for an HDE, companies submit an HDE application to FDA, which has special requirements. This hard cap at 4,000 individuals is excessively restrictive. Provisions related to the statutory cap continue to be interpreted very narrowly by FDA and block the development of diagnostic devices for rare diseases and conditions. There is no scientific evidence behind the original statutory 4,000 person cap. In particular, it is a significant hurdle for the development of diagnostic devices for rare diseases to demonstrate the number of patients that would be subject to diagnosis by the device, rather than the number of individuals affected or manifesting the rare disease. If a diagnostic test were developed to diagnose patients with a condition that manifests in 4,000 people or less per year, it is quite likely that physicians would prescribe the test more than 4,000 times a year to diagnose those with the rare disease.

To address this limitation, we recommend flexibility to FDA to allow HDEs that benefit patient populations that exceed the 4,000 limit. Applicants would be required to demonstrate that the severity



of the disease or condition is such that the public health requires a greater availability of the device to treat or diagnose that population. This provision clarifies that in the case of IVDs, the 4,000 person limit does not apply to the number of tests needed to treat or diagnose a specific patient population.

With respect to the current emergency use authorization process, we note it has yielded a number of new tests (e.g., Ebola most recently) to meet public health needs and was greatly improved when, on March 13, 2013, President Obama signed into law the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA). PAHPRA built on the availability and use of an unapproved medical product (such as a diagnostic test) and the unapproved use of an approved medical product during or before an emergency to diagnose, treat, or prevent a serious life-threatening disease. Other available FDA pathways to meet unmet needs and promote development of emerging diagnostics should be explored when appropriate and vigorously placed in use in the review process to support diagnostics innovation and the public health. Improving the HDE process for diagnostics tests should be first in order if we are to support development of rare disease diagnostics for patients.

#### ***10) Transition Process for Diagnostics Under a Modernized Regulatory System***

As articulated in earlier responses, we believe FDA should oversee the safety and effectiveness of all diagnostics, including LDTs. A test is a test and presents the same risk for patients regardless of whether it is developed by a manufacturer or a laboratory. Potential harms to patients whose tests return incorrect results include unnecessary treatments with their accompanying costs and side effects and treatment delay or failure to obtain appropriate treatment, all of which lead to worse outcomes for those patients.

The degree of regulation needed to ensure the safety and effectiveness of diagnostics should be determined by the risk that tests present to patients rather than by arbitrary grandfathering or carve-outs that do not take into account patient risk, particularly of potential harms resulting from the use of higher risk tests. Tests present the same risk/benefit profile for patients no matter where a test is made.

We commend FDA's commitment to the thoughtful development of a proposed risk based LDT oversight framework that reflects a number of features to ease transition for the laboratory community and support test continuity. Key elements of the proposed framework include a risk based approach, phase in over a 9-year time frame, and continued use of enforcement discretion for many LDTs to minimize disruption and support test continuity. Also, tests undergoing premarket review may notably remain on the market during the review process, which will aid transition of tests under FDA oversight.

We strongly support transitioned requirements to facilitate good faith efforts for laboratories. Furthermore, we would encourage meaningful discussion of ways in which laboratories can be aided in this endeavor and additional measures that might be implemented for diagnostics at large to support robust innovation now and into the future. As previously referenced, opportunity is also ripe as part of FDA regulatory efforts aimed at higher risk tests and implementation of an overall modernized framework to consider appropriate additional exemptions from premarket review of low-risk, well-established diagnostics tests regardless of developer. This would best leverage FDA resources and help pave the way for an overall improved risk based regulatory process for all diagnostics.



Other available FDA pathways to promote development of new cleared and approved diagnostic technologies, such as a transitional approach for emerging diagnostics, should be implemented to aid the regulatory process and support good faith efforts by developers of innovative diagnostic technologies.

### ***11) Overall Incentives to Encourage Development of New or Improved Diagnostics Tests***

In summary, AdvaMedDx has long advocated for a flexible, risk based approach for all diagnostics. Maintaining two very different oversight mechanisms for tests that are the same from the perspective of patient safety is bad public policy, provides an opportunity to use tests in clinical settings without sufficient clinical data, and stifles investment in high quality products that can stand up to FDA review. It is imperative that the FDA adopt a risk based regulatory approach for all diagnostics, regardless of where a test is developed. We believe a proper oversight system that balances both patient safety and continued and future innovation can be accomplished under appropriate risk based oversight by FDA.

While FDA has made tremendous progress in improving the regulatory process for diagnostics and its recent proposed framework for LDTs is a critical step forward, we have noted opportunities to improve the overall diagnostics landscape. In addition to focusing on tests that pose higher risk to patients, FDA should strive to expedite patient access to lower risk tests—regardless of where made—by more efficient use of the premarket review process, including additional exemptions for well-established tests. Efforts must also be undertaken by FDA to ensure that data submission requirements are commensurate with the level of risk of the test. Reviewer training continues to be critical with respect to FDA application of a least burdensome approach to ensure requiring only the evidence necessary to evaluate all IVD submissions. FDA should also continue to leverage available pathways to support bringing new safe and effective products to market and seek to continuously improve the regulatory process for all diagnostics.

In particular, we welcome discussion of how to best assure patient access to rare disease diagnostics. FDA's application of the HDE pathway has been a significant obstacle for the development of diagnostic devices and must be improved to serve as a meaningful pathway for developers of rare disease diagnostics.

AdvaMedDx appreciates the opportunity to work with Chairman Upton, Representative DeGette, and the Energy and Commerce Committee on the 21st Century Cures initiative. We greatly appreciate the Committee's commitment to improving patient care and assuring a modernized diagnostics regulatory framework. We would welcome additional dialogue on any of the concepts presented in response to this request for feedback on the questions posed and are happy to answer any questions on these or other diagnostics issues. U.S. diagnostic innovation is shaping the lives of Americans as well as the greater global community. As innovators, our member companies know well that robust investment in safe and effective diagnostic technologies is critical to the timely development of life-changing diagnostics, treatments, and cures, and sound public policy is essential to sustaining that investment by promoting public health and innovation.

To the members and staff of the Energy & Commerce Committee:

On behalf of the American College of Cardiology (ACC), a 47,000-member medical society that is the professional home for the entire cardiovascular care team, I am pleased to provide our feedback on your white paper concerning the review and oversight of laboratory developed tests (LDTs).

While the ACC does not have standing policy on this topic of sufficient depth to answer each of the questions posed, we feel the following principles pertaining to LDTs are necessary guideposts to safeguard the provision of the highest quality cardiovascular care:

- Innovation plays an essential role in the continued availability of cutting edge treatments and the improvement of patient outcomes. Great care must be taken to ensure that policy changes remove barriers to innovation while taking necessary measures to ensure public safety.
- The clinician-patient relationship is of central importance to the provision of quality medical care. Direct-to-consumer marketing can cause unnecessary harm by subjecting patients to clinical information that requires clinician involvement for proper interpretation. For this reason, we feel strongly that direct-to-consumer marketing should be heavily restricted.
- To ensure proper scrutiny, any changes to LDT policy should be subjected to the regular rulemaking process.

Thank you again for the opportunity to comment on this issue. We look forward to further discussion as the 21<sup>st</sup> Century Cures Initiative moves forward.

Best,  
Nick

Nick Morse  
Director, Congressional Affairs  
American College of Cardiology



Chairman of the Board  
Bernard P. Dennis

President  
Elliott M. Antman, MD, FAHA

Chairman-elect  
Alvin L. Royse, JD, CPA

President-elect  
Mark A. Creager, MD, FAHA

Immediate Past  
Chairman of the Board  
Ron W. Haddock

Immediate Past President  
Mariell Jessup, MD, FAHA

Treasurer  
David A. Bush

Directors  
Mary Ann Bauman, MD  
Mary Cushman, MD, MSc, FAHA  
Mitchell S. V. Elkind, MD, MS, FAHA  
Robert A. Harrington, MD  
Steven R. Houser, PhD, FAHA  
Marsha Jones  
Willie E. Lawrence, Jr., MD, FAHA  
Pegui Mariduena, CMC, MBA  
John J. Mullenholz  
Bertram L. Scott  
David A. Spina  
Bernard J. Tyson  
Raymond P. Vara, Jr.  
John J. Warner, MD  
Alexander P. Almazan, PA - Liaison  
James J. Postl - Liaison

Chief Executive Officer  
Nancy A. Brown

Chief Mission Officer  
Meighan Girgus

Chief Diversity Officer  
Gerald Johnson, II

Chief Administrative Officer &  
Chief Financial Officer  
Sunder D. Joshi

Chief Science & Medical Officer  
Rose Marie Robertson, MD, FAHA

Chief Development Officer  
Suzie Upton

Chief of Staff to the CEO  
Laura Sol

Deputy Chief Medical Officer  
Eduardo Sanchez, MD, MPH

Executive Vice President,  
Corporate Secretary &  
General Counsel  
Lynne M. Darrrouzet, Esq.

Advocacy Department  
1150 Connecticut Ave., NW | Suite 300 | Washington, DC 20036  
P 202-785-7900 | F 202-785-7950 | www.heart.org

January 5, 2015

Committee on Energy and Commerce  
2125 Rayburn House Office Building  
Washington, DC 20515

Re: Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests

Dear Chairman Fred Upton and Ranking Member Frank Pallone, Jr.:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and over 22.5 million volunteers and supporters across the country, we appreciate the opportunity to provide comments to the Committee on Energy and Commerce regarding the regulation of laboratory developed tests (LDTs).

We also appreciate the attention the Committee has given this issue as part of its 21<sup>st</sup> Century Cures Initiative and its work to engage stakeholders to ensure the proper regulation of LDTs. We were grateful for the opportunity to provide testimony at the Subcommittee on Health's hearing on September 9, 2014, and we thank the Committee for providing additional opportunities for us to share our concerns about the lack of enforcement of regulation on LDTs.

We support the FDA's recently released draft guidance documents and its proposed approach for regulating LDTs in a phased-in, risk-based manner. We believe this is the best approach for ensuring the appropriate level of oversight for LDTs in order to reassure patients and providers on the reliability and usefulness of these tests.

Genetic and genomic tests have become increasingly integrated into health care in the United States for the diagnosis and treatment of cardiovascular disease (CVD), but there is still work to be done in developing testing for complex forms of CVD that have many genetic and environmental

factors.<sup>1</sup> As patients and doctors become more reliant on genetic tests, it is critical that their validity, accuracy, safety, and effectiveness is assured by the FDA. This is why we support FDA's proposal and strongly encourage Congress to allow the FDA to move forward with its process for finalizing and implementing its guidance documents.

The AHA is not alone in expressing concerns about LDTs and the need for oversight by the FDA. In a report issued in 2000 from the Secretary of the Department of Health and Human Services' (HHS) Advisory Committee on Genetic Testing, it concluded that genetic tests should not be introduced in the market before it is established that they can be used to diagnose or predict health-related conditions.<sup>2</sup> A 2006 Government Accountability Office (GAO) report found that tests from four companies that offered genetic testing services directly to the market and consumers without independent verification provided results – which included future risk of heart disease and high blood pressure – that were medically unproven, meaningless, and misleading.<sup>3</sup> A 2008 HHS Secretary's Advisory Committee on Genetic Health and Society report also expressed concerns about gaps in oversight and recommended that the “FDA should address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests.”<sup>4</sup> In 2010, GAO again found companies that marketed genetic tests directly to consumers and provided direct access to genetic testing services misled consumers and their tests offered results that were of “little or no practical use.”<sup>5</sup>

The lack of appropriate oversight detailed throughout each of these reports demonstrates there is no guarantee of test quality and performance for LDTs and that doctors – attempting to make an accurate diagnosis or prediction of risk – and patients – interested in reducing their risk for disease – may receive and take action based on an inaccurate or misleading result. The release of the FDA's draft oversight guidance is an important step towards addressing these problems and balancing the needs of protecting patients while allowing developers to innovate and discover potentially groundbreaking advances in the diagnosis and treatment of CVD.

### Defining Risks

We agree with the FDA's risk-based approach and believe it provides the best way for setting clear parameters for developers of new tests that would allow for the continued advancement of highly complicated, potentially groundbreaking discoveries while ensuring their clinical validity and reducing risks to patients. In defining risks, we believe that the risks of harm are greater when testing is ordered by the consumer and not

---

<sup>1</sup> Ganesh et al. *Circulation*. 2013; 128: 2813-2851.

<sup>2</sup> Secretary's Advisory Committee on Genetic Testing. *Enhancing the oversight of genetic tests: recommendations of the SACGT*. Bethesda, MD: National Institutes of health. 2000.

<sup>3</sup> US Government Accountability Office. “Nutrigenetic testing: tests purchased from four websites mislead consumers [testimony before the Special Committee on Aging, US Senate].” Washington, DC: US Government Accountability Office. 2006.

<sup>4</sup> Ferreira-Gonzalez et al. *Personalized Medicine*. 2008; 5:521-528.

<sup>5</sup> US Government Accountability Office. “Direct-to-consumer genetic tests: misleading test results are further complicated by deceptive marketing and other questionable practices.” Washington, DC: US Government Accountability Office. 2010.

by a health care professional and believe that all disease-based direct-to-consumer testing should be considered moderate-to-high risk. AHA also believes that low-risk, Class I LDTs should be defined as those tests for which there is a well-established scientific consensus on the validity and utility of the test, where the agency believes that the probability of a false result is low, and where there is little risk to patients from a false result. We also believe that the FDA is providing significant transparency as it seeks to classify LDTs. AHA appreciates that the FDA will provide additional guidance to describe what it generally considers to be Class I, II or III within 24 months from finalization of its guidance and supports FDA's decision to use advisory panels as part of the process for prioritizing and categorizing LDTs.

### CLIA vs. FDA Oversight

We understand that there are concerns that FDA oversight will overlap with existing requirements under the Clinical Laboratory Improvement Amendments (CLIA). However, it is important to remember that the CLIA approval process ensures only the analytic validity, or accurate measurement, but fails to address clinical validity. CLIA does not address whether or not a test result is clinically important to a patient's health decision-making. Additionally, CLIA does not require premarket review, does not require adverse event reporting systems for tests that cause or contribute to a death or serious injury or has malfunctioned, and does not have a process for correcting problems that may cause an unreasonable risk of harm to the public health. A 2013 FAQ by the Centers for Medicare and Medicaid Services (CMS), the agency that oversees CLIA, explains these differences and explicitly states that FDA's and CLIA's "regulatory schemes are different in focus, scope, and purpose."<sup>6</sup>

### Transitioning to Oversight

We also recognize concerns that FDA oversight may create transition challenges and that the agency may face a burden reviewing all genetic tests currently on the market. We believe, however, that the FDA's phased-in, risk-based approach provides sufficient flexibility to laboratories and would allow the agency to prioritize the highest-risk tests first to overcome these challenges. For example, the FDA plans to continue enforcement discretion with respect to applicable premarket submission requirements for LDTs classified as Class I devices, as well as those considered traditional LDTs, LDTs for unmet needs, and LDTs for rare disease. The FDA also intends to continue to exercise enforcement discretion for LDTs while premarket submissions are under FDA review, and it does not anticipate fully phasing-in enforcement of premarket regulatory requirements for Class II and Class III LDTs for at least 9 years. These elements of the draft guidance, in addition to its open process for classifying LDTs, will allow laboratories to be well prepared in advance of any FDA oversight.

---

<sup>6</sup> CMS. LDT and CLIA FAQs. 2013. Accessed December 30, 2014: [http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA\\_FAQs.pdf](http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf)

## Regulatory Incentives

We also agree with the Committee that incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests. This is particularly important as the science is still evolving for many genetic tests, and we anticipate that laboratories may identify ways to improve tests that have already been cleared or approved by the FDA. This is why we plan on recommending to the FDA that it provide a mechanism for expediting the review of such improvements of approved and cleared tests.

## Conclusion

Again, we are encouraged by the steps taken by the FDA to oversee LDTs. We hope that the Committee and Congress will support the agency and allow it to act swiftly to finalize its guidance and phase-in regulation of these tests. The American Heart Association looks forward to providing continued assistance to the Committee and FDA in support of this endeavor. If you have any questions or need any additional information, please do not hesitate to contact Kevin Kaiser, Government Relations Manager, at 202-785-7931 or via email at [kevin.kaiser@heart.org](mailto:kevin.kaiser@heart.org).

Sincerely,

A solid black rectangular redaction box covering the signature area.

Sue Nelson  
Vice President of Federal Advocacy  
American Heart Association



**ASSOCIATION FOR MOLECULAR PATHOLOGY**  
*Education. Innovation & Improved Patient Care. Advocacy.*  
9650 Rockville Pike. Bethesda, Maryland 20814

Tel: 301-634-7939 | Fax: 301-634-7995 | [amp@amp.org](mailto:amp@amp.org) | [www.amp.org](http://www.amp.org)

January 5, 2015

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.

---

<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.

[http://nvca.org/index.php?option=com\\_docman&task=doc\\_download&gid=668&Itemid=93](http://nvca.org/index.php?option=com_docman&task=doc_download&gid=668&Itemid=93)

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

[http://www.amp.org/publications\\_resources/position\\_statements\\_letters/PRC/H1N1Statement.pdf](http://www.amp.org/publications_resources/position_statements_letters/PRC/H1N1Statement.pdf)



**Alliance for Natural Health USA**

Piedmont Center, Building 5  
3525 Piedmont Rd NE, Suite 110  
Atlanta, GA 30305

email: [office@anh-usa.org](mailto:office@anh-usa.org)  
tel: 800.230.2762  
202.803.5119  
fax: 202.315.5837  
[www.anh-usa.org](http://www.anh-usa.org)

ANH-USA is a regional office of ANH-Intl

**INTERNATIONAL**  
[anhinternational.org](http://anhinternational.org)

January 5, 2015

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

The Honorable Diana DeGette  
Member  
House Energy and Commerce Committee  
2125 Rayburn House Office Building  
United States House of Representatives  
Washington, DC 20515

Via Electronic Mail to [cures@mail.house.gov](mailto:cures@mail.house.gov)

**Re: Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests**

Dear Chairman Upton and Congresswoman Degette:

The Alliance for Natural Health USA (“ANH-USA” or “we”) supports the focus of the 21st Century Cures initiative on personalized medicine in the effort to accelerate the pace of cures in the United States. Laboratory developed tests (“LDTs”) are a crucial component to providing effective individualized medicine, and we hope Congress will act to protect access to this essential health care tool. ANH-USA writes to offer comments on the white paper, *“21st Century Cures – Request for Feedback: a Modernized Framework for Innovative Diagnostic Tests.”*

ANH-USA is a nonprofit corporation founded in 1992. ANH-USA is a membership-based organization consisting of over 400,000 consumers, healthcare practitioners, and food and dietary supplement companies. ANH-USA protects and promotes citizen access to information concerning the interaction between health and the environment, as well as the benefits of food, lifestyle choices and dietary supplements. Through public education, ANH-USA arms consumers with the tools they need to make informed, individualized decisions and to take personal responsibility for their health. Our ultimate goal is to promote disease prevention, reduce medical intervention, and reduce the public cost of healthcare in the United States.

ANH-USA would like to reiterate two essential points that have been raised by numerous other stakeholders. First, the Food and Drug Administration (“FDA” or the “Agency”) lacks the statutory authority to regulate LDTs. Second, if it is determined conclusively that FDA does have such authority, new regulations should be promulgated via the formal rulemaking process rather than through guidance. Consequently, we respectfully urge the Committee to act promptly to instruct FDA to halt its current course of action.

The question regarding FDA’s authority to regulate LDTs has been an ongoing point of contention that needs to be resolved. Two organizations, the Washington Legal Foundation and the American Clinical Laboratory Association, independently submitted petitions challenging FDA’s authority to regulate LDTs. On July 31, 2014, FDA rejected both petitions by unequivocally stating it could regulate LDTs as devices. However, this did not resolve the issue, as reflected by the concern expressed and questions asked by members of the Subcommittee on Health at the September 9, 2014 hearing on the draft LDT guidance documents. Additionally, in a November 18, 2014 letter to Dr. Margaret Hamburg, Commissioner of FDA, a large group of stakeholders pointed to the question of whether FDA has the statutory authority to regulate LDTs as “a matter of significant legal controversy.” With so much at stake, the Committee would be wise to advise FDA to stop the guidance process until the issue can be resolved in a definitive manner. It is ANH-USA’s position that FDA does not have the requisite statutory authority to regulate LDTs, and we believe the Agency’s recent action on LDTs is an overstep that must be addressed by Congressional action.

Additionally, for regulatory changes having such significant, widespread impact, FDA should engage in the formal rulemaking process rather than issue new regulations through informal guidance, which is non-binding and expresses only FDA’s preferences and interpretations. Although employing guidance enables the Agency to avoid requirements such as the need to respond to every substantive comment and do an economic impact analysis, it still would be beneficial to the Agency, as well as stakeholders, to use formal rulemaking for the proposed enforcement policy. This is especially true given that on the October 23, 2014 webinar hosted by the Center for Devices and Radiological Health, the Agency indicated that it plans to address all comments it receives during the comment period. (*Transcript of Webinar: Framework for Regulatory Oversight of LDTs Draft Guidance*, NWX-HHS FDA (US), at p. 16 (Oct. 23, 2014)). If FDA intends to respond to all comments, as mandated in the formal rulemaking process, using the notice-and-comment process would eliminate a potential grounds for legal challenge and thus remove a possible source of delay in the implementation process. Additionally, an economic impact analysis is a crucial component of the discussion regarding LDTs and is not mentioned in any way in the draft guidance documents.

In conclusion, LDTs are the future of medicine and must be protected by Congress through carefully considered legislative action. It is crucial that innovation be fostered while at the same time, patients’ access to potentially life-saving tests be protected. The magnitude of the effects of FDA’s draft guidance on LDTs cannot be understated. As a

result, we encourage Congress to continue engaging in the process of determining what the rules for regulating LDTs should be.

Sincerely,

A black rectangular redaction box covering a handwritten signature in blue ink.

Gretchen DuBeau, Esq.  
Executive and Legal Director  
Alliance for Natural Health USA



American Society of Clinical Oncology

**PRESIDENT**

Peter P. Yu, MD, FASCO

**IMMEDIATE PAST PRESIDENT**

Clifford A. Hudis, MD, FACP

**PRESIDENT-ELECT**

Julie M. Vose, MD, MBA, FASCO

**TREASURER**

Susan L. Cohn, MD

**DIRECTORS**

Smita Bhatia, MD, MPH

Charles D. Blanke, MD,  
FACP, FASCO

Linda D. Bosserman, MD, FACP

Walter J. Curran, Jr., MD, FACP

Stephen S. Grubbs, MD

Paulo M. G. Hoff, MD, FACP

Hagop M. Kantarjian, MD

David Khayat, MD, PhD, FASCO

Gary H. Lyman, MD,  
MPH, FASCO

Neal J. Meropol, MD, FASCO

Therese M. Mulvey, MD, FASCO

Carolyn D. Runowicz, MD,  
FASCO

Lillian L. Siu, MD, FRCPC

Eric P. Winer, MD, FASCO

**EX-OFFICIO MEMBERS**

Allen S. Lichter, MD, FASCO  
*ASCO Chief Executive Officer*

W. Charles Penley, MD, FASCO  
*Chair, Conquer Cancer  
Foundation Board of Directors*

January 5, 2015

The Committee on Energy and Commerce, Health Subcommittee  
House of Representatives  
2125 Rayburn House Office Building  
Washington, DC 20515

Re: Response to House Energy and Commerce Committee on Regulation of  
Laboratory-Developed Tests

Submitted electronically to [cures@mail.house.gov](mailto:cures@mail.house.gov).

To whom it may concern:

The American Society of Clinical Oncology (ASCO) appreciates the opportunity to provide feedback to the House Energy and Commerce Committee on the regulation of laboratory developed tests (LDTs). ASCO is a national organization representing over 35,000 physicians and other healthcare professionals specializing in cancer treatment, diagnosis and prevention. ASCO members also are dedicated to conducting research that leads to improved patient outcomes, and we are committed to ensuring that evidence-based practices for the prevention, diagnosis and treatment of cancer are available to all Americans. We value the chance to contribute to this discussion on behalf of our members.

ASCO strongly supports the FDA's proposed risk-based approach to regulation of LDTs, particularly genomic tests that, increasingly, are being used to guide therapy selection for patients with cancer. Failure of such tests to perform as intended can lead to patients receiving an inappropriate and potentially harmful treatment or, alternatively, not receiving a treatment that has the potential to benefit them. At the same time, ASCO also strongly recommends that this regulation be implemented in such manner as to ensure ongoing innovation in the field of molecular testing as well as timely patient access to the scientific advances which can improve their care.

Prevailing regulations that apply to LDTs offered for clinical use, namely the Clinical Laboratory Improvement Amendments (CLIA), do not directly assess the safety and effectiveness of LDTs offered by laboratories. Rather, they determine that the laboratory follows generally accepted standards for good laboratory practices. Under CLIA, laboratories are required to demonstrate the analytical validity of the tests they offer, that is, that the test accurately and reproducibly measures what it claims to measure. However, analytical validation of LDTs

2318 Mill Road, Suite 800  
Alexandria, VA 22314  
T: 571-483-1300  
F: 571-366-9530  
[www.asco.org](http://www.asco.org)

*Making a world of difference in cancer care*

under CLIA is not as comprehensive as that required by FDA, and is not designed to ensure consistent performance for measuring the same analyte across laboratories. Moreover, CLIA does not evaluate the clinical validity of a test, i.e., the test's ability to detect the clinical condition for which the test is intended. Nor does CLIA evaluate the clinical utility of the test, i.e., whether or not patient outcomes are improved by using the test.

In contemporary oncology practice, a patient's treatment options are increasingly driven by detection of molecular abnormalities in the tumor that drive treatment selection. ASCO believes that the tests used to detect those abnormalities must be of the highest quality and thoroughly validated before being offered to doctors and patients. Our patients depend on high quality tests as much as they depend on carefully studied, safe and effective drugs to achieve the best possible outcomes.

ASCO appreciates the Committee's interest in LDT regulation and offers the following responses to questions posed in the white paper "A Modernized Framework for Innovative Diagnostic Tests":

*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?*

Diagnostic tests that are marketed and sold as kits and/or devices are currently regulated by FDA. These may be used in the laboratory setting or the practice setting. Laboratory developed tests are developed and performed by trained individuals operating in a CLIA-certified environment. Current FDA draft guidance provides a framework for regulation of these tests that would not require a significant burden of proof or administrative effort for low and medium risk tests. It is appropriate to closely regulate high risk tests as these influence clinical decisions that could result in significant harm or death if the improper course of treatment is administered. A high-risk LDT performed in any setting (central laboratory, hospital-based laboratory, or practice) should be carefully regulated because of the implications for the patient.

A test should be considered under development if there is not a standardized protocol and adequate proof of analytic validity. In addition, for high-risk tests, ASCO recommends that standards for analytical validation address the need for consistent performance for the same marker(s) across testing laboratories, as well as requirements for evidence supporting clinical validity.

Diagnostic tests developed for clinical use should have a clearly stated intended use that addresses an unmet medical need. The final test product or procedure should be fit for purpose, that is, it should assess the analytes of interest in the specimens of interest obtained from individuals with the clinical state of interest. All test procedures should be well validated, finalized, and thoroughly documented so that the test can be adequately reproduced across laboratories and these principles should apply to both the manufacturing and conduct of laboratory tests. ASCO does not believe that these general principles of test development and

performance constitute the practice of medicine but, rather, represent good laboratory and manufacturing practices. The practice of medicine includes the interpretation of clinical implications of the test results in the context of the overall clinical management of the patient but the utility of test results by the clinician depends to a great extent on its analytical and clinical validity as described above.

Having said that, one factor in deciding whether an LDT is a high risk test is whether it provides guidance on selection of treatment, or may be interpreted as doing so. Terms such as “actionable” are ambiguous and must be strictly defined or avoided. A clear distinction must be made between the practice of medicine and use of an LDT, especially when the LDT report includes discussion of therapies that are not FDA approved indications, listed in CMS approved compendium or supported by publications in two peer-reviewed journals approved by the Secretary of Health and Human Services. Simply reporting test results is not the practice of medicine, but providing accompanying guidance on treatment selection, especially when the basis for that guidance is neither sufficiently rigorous nor transparent, may cross the boundary of the practice of medicine.

*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?*

Current statute defines an *in vitro* medical device as “those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body” (21 CFR 809.3(a)). ASCO believes that this is a clear definition that applies to tests developed in laboratory settings.

ASCO has long advocated for clarity in the regulation of tests so that patients have access to reliable, high quality tests for making treatment decisions. ASCO supports the definition of LDT contained in the FDA draft guidance, “laboratory developed test (LDT) as an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory.” ASCO supports the risk-based approach to regulation of these devices as proposed in the guidance document.

*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?*

FDA currently uses a classification system to determine levels of evidence required for the marketing of therapeutic medical devices. This classification system has been used for decades

to safely and appropriately regulate devices based on the level of risk they pose a patient should the device malfunction. The Food, Drug and Cosmetic Act defines a class III (or high risk) device as one that “is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury.” This definition is appropriate for diagnostic tests as well, specifically for tests intended for treatment selection. Unlike drugs or therapeutic medical devices that pose risks to patients due to toxicity, malfunction or failure to perform as intended, high risk *in vitro* diagnostic tests pose significant risks to patients in that inaccurate results could lead patients and physicians to choose treatment options that do not appropriately treat the underlying disease. This could result in treatments that expose patients to risk and harm while allowing the disease to progress unabated. These risks are potentially greater for LDTs compared to distributed test kits because LDTs do not currently undergo pre-market review or have a clearly defined path for reporting of adverse events.

*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?*

Yes. As our understanding of molecular abnormalities that underpin cancer and other diseases increases, tests based on molecular profiling will have a greater impact on the diagnosis, prognosis, treatment and monitoring of disease. It is extremely important that patients receive high quality diagnostic tests as these increasingly drive treatment decisions including whether to begin treatment, what treatment to use and when to modify treatment. ASCO supports pre-market review of high risk (class III) devices to ensure safety and effectiveness and believes that the current FDA standards and practice that apply to all medical devices are appropriate for test kits and LDTs as well.

*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?*

Under FDA’s proposed guidance, high risk (class III) tests will require pre-market review. As the outcomes of these tests can lead to treatment decisions that could significantly impact patient health, it is vital that these diagnostic tests are safe, effective and of high quality. Post-market controls are important to monitor safety and discover unusual or rare adverse events. It is not appropriate to rely solely on post-market review to ensure the safety and effectiveness of high risk tests. The current FDA draft guidance strives to balance patient risk and access to new diagnostic tests by taking into account established scientific literature on clinical validity, the role of expert interpretation of a test, and the phased-in approach to LDT regulation. ASCO strongly supports efforts to ensure timely patient access to valuable new diagnostic tests, including the use of post-market controls, and recommends that these considerations be given high priority in the implementation of LDT regulation.

*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?*

Tests are often modified to conform with the standard procedures, workflow, or availability of reagents or equipment in individual laboratories. LDTs should be held to the same standard as distributed test kits with respect to requirements for supplemental clearance or approval. Modifications in sample handling or preparation should not require supplemental clearance or approval, but the individual laboratory must be able to rigorously demonstrate that the modifications do not affect the accuracy or precision of the test. Modifications that alter the method of detection or analysis of a molecular abnormality may constitute a significant change in the test and therefore should require submission of a supplemental clearance or approval prior to implementation. In addition, a change in the intended use of the test likely also constitutes a significant change that requires a supplemental premarket submission.

*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?*

Labeling requirements for *in vitro* diagnostic tests is currently established in statute ([21 CFR 809.10](#)) and should apply to most LDTs. The label conveys essential information about the protocols, specimen handling, storage, safety considerations, methodology, biological basis, and interpretation of the test and its components, based upon available data for analytical performance and clinical validity. This information ensures the proper use and interpretation of an *in vitro* diagnostic test and should be made publicly available when the LDT is approved (for high risk tests) or after registration and listing (for lower risk tests). Laboratories that modify tests without obtaining a supplemental clearance or approval should make patients, providers and payers aware of aspects of the protocol that have been changed and how those changes impact the performance of the test for its intended use. Tests that are modified such that supplemental clearance or approval is required should carry a new, revised label.

ASCO believes that information provided to the individual patient or health care provider should be clear and easily interpretable. The use of standard formats, consistent nomenclature, and context in lay language is important but regulatory oversight may not be the most efficient method of implementation. ASCO plans to work with professional societies that represent pathologists to develop recommendations for best practices in the reporting of test results to patients and health care providers.

*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)?*

A regulatory system must take into account the ability to obtain data to validate tests as well as the potential risks and benefits to patients and the population as a whole. When considering diagnostic tests in the context of rare diseases, ASCO believes that “rare” should depend on the frequency of use of the test, rather than the occurrence of the disease in the general population. For example, non-small cell lung cancer (NSCLC) is a common cancer, but only about 4% of NSCLC tumors harbor an ALK mutation. While ALK positive NSCLC may be a rare disease, the test for the presence of an ALK mutation is not, as it is a common diagnostic test for NSCLC patients. This distinction is important, as a widely applied test for a “rare” condition should be held to a high standard for rigor. Moreover, infrequent use of a test by a particular laboratory may negatively impact the reproducibility of the results. A regulatory system must properly balance the limited data available to determine clinical validity and the need to ensure ongoing analytic validity for rare tests.

With respect to diagnostic tests for unmet needs or public health emergencies, a regulatory system must be flexible enough to do an accurate risk/benefit analysis with respect to the needs of individual patients and the general public – just as the Agency does when it comes to therapies and vaccines. Oncology products often address unmet medical needs and ASCO has observed that in general FDA has been flexible, reasonable and increasingly timely in product approvals. The current draft guidance contains provisions that allow continued flexibility in the approval of diagnostic tests. This flexibility is particularly important in oncology as new information develops rapidly and is disseminated widely leading to demand by both physicians and patients for new tests that impact medical decision-making. An important role of LDT providers has been to rapidly introduce new tests in response to emerging medical information, and it is important that any new regulatory framework for LDTs preserve the ability of test developers to respond quickly to medical needs for the benefit of patients even while regulatory submission is being prepared and regulatory review is ongoing.

*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?*

ASCO believes that changes in regulatory systems should involve a clearly delineated process and a sufficient timeline to minimize disruption to patients, healthcare providers, laboratories, innovators and the marketplace. Existing diagnostic tests should not be grandfathered, as it could create a confusing marketplace where some tests for the same condition or biological marker have been reviewed for their analytic and clinical validity while others have not. This difference may not be apparent to patients or health care providers, and there is the chance of high-risk treatment decisions being made based on a test that was mistakenly thought to have obtained regulatory clearance or approval. Existing diagnostic tests should be subject to the same requirements as new tests. Existing high-risk tests should remain on the market during “premarket review” and then reflect approval or be removed from the market after review. The

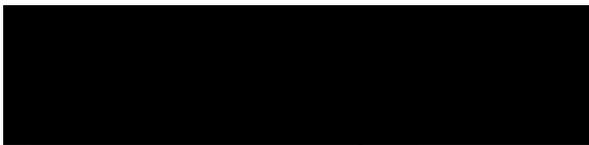
review of existing tests should be scheduled equitably such that similar tests are reviewed concurrently. The phased approach in the FDA draft guidance seems appropriate and should provide ample time for test providers to comply.

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

Diagnostic test labels should explicitly include a statement on the level of evidence considered in the premarket review. For example, one test may include in the label that it had evidence to support clinical utility, while another for the same marker may only have demonstrated analytic validity. This information would inform patients, health care providers and payers about which tests have evidence to support their use in specific circumstances. For some applications, it may be reasonable to choose a low-cost test while in high-risk settings (i.e. where treatment decisions are contingent on test results), the test with the most robust evidence base may be necessary. Reimbursement rates would then be aligned with the desired level of evidence for a test. These decisions, in aggregate, should influence test developers to focus on efficiency in some areas and in others take on the extra time and expense to ensure higher accuracy and clinical validity.

Thank you for the opportunity to provide this feedback. ASCO would be pleased to provide additional information on these comments, or collaborate on developing these ideas further. If you have any questions in the future, please do not hesitate to contact Kristin McDonald at [kristin.mcdonald@asco.org](mailto:kristin.mcdonald@asco.org) (571-483-1642).

Sincerely,



Peter P. Yu, MD, FASCO  
President  
American Society of Clinical Oncology



200 First Street SW  
Rochester, Minnesota 55905  
507-284-2511  
mayoclinic.org

January 5, 2015

Chairman Fred Upton  
Representative Diana DeGette  
Co-Chairs, 21<sup>st</sup> Century Cures Initiative  
C/O House Energy and Commerce Committee  
2125 Rayburn House Office Building  
Washington, DC 20515

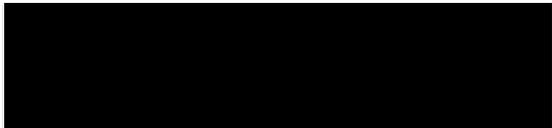
Dear Chairman Upton and Rep. DeGette,

On behalf of Mayo Clinic, our clinical and academic Department of Laboratory Medicine and Pathology, and Mayo Medical Laboratories, please see the attached submission of our response to the 11 questions posed by you and your 21<sup>st</sup> Century Cures staff pertaining to potential Food and Drug Administration (FDA) oversight of Laboratory Developed Tests.

We thank you for the opportunity to participate in the dialogue, and hopefully contribute to the solution of how best to ensure safe, effective, and accurate test results to all patients.

If we can be of further assistance to you, the Initiative, and the Energy and Commerce Committee, please contact Jennifer Mallard, Mayo Clinic's Director of Federal Government Relations at 202-621-1850 or [mallard.jennifer@mayo.edu](mailto:mallard.jennifer@mayo.edu).

Sincerely,



Curt Hanson, M.D.  
Chair, Mayo Clinic Department of Laboratory Medicine and Pathology  
President and CEO, Mayo Medical Laboratories

**STATEMENT**  
**of the**  
**Mayo Clinic – Department of Laboratory Medicine and Pathology**  
**and**  
**Mayo Medical Laboratories**  
**For the Record**  
**U.S. House of Representatives**  
**Committee on Energy and Commerce**  
**Subcommittee on Health**  
**Re: 21<sup>st</sup> Century Cures—Request for Feedback:**  
**A Modernized Framework for Innovative Diagnostic Tests**

**January 5, 2015**

The Mayo Clinic commends the U.S. House of Representatives Committee on Energy and Commerce Subcommittee on Health's (Subcommittee) efforts to build on and accelerate wide-spread clinical application of innovative tests. We welcome the opportunity to respond to the questions posed by the Subcommittee and we believe that this is an opportunity to modernize the regulatory environment for the clinical diagnostic laboratory.

Mayo Clinic is a nonprofit worldwide leader in medical care, research, and education for people from all walks of life. Every year, more than one million people from all 50 states and nearly 150 countries come to Mayo Clinic for care. We have approximately 4,150 staff physicians and scientists; 3,150 residents, fellows, and students; and 52,200 allied health staff (clinic and hospital) who work at locations in Rochester, Minnesota; hospitals and clinics throughout southeast Minnesota and southwest Wisconsin; Scottsdale, Arizona; and Jacksonville, Florida. For more than 150 years, Mayo's unique style of care brings teams of experts together to provide high-quality, compassionate care to our patients.

Mayo Medical Laboratories (MML) is a global reference laboratory operating within Mayo Clinic's Department of Laboratory Medicine and Pathology. This department maintains a robust diagnostic test-development program, launching more than 150 new tests each year. Within MML, more than 20 million tests are performed annually for more than 4,000 health care organizations around the world. Based on Mayo's integrated group practice, our services enable health care institutions and providers to collaborate directly with Mayo Clinic physicians, scientists, and laboratory professionals to expand the knowledge of, and access to, the latest testing and treatment guidance for patients in need.

The U.S. Food and Drug Administration (FDA) has announced its intent to exert regulatory oversight of Laboratory-Developed Tests (LDTs). Clinical laboratories are highly regulated and required to meet the standards of the Clinical Laboratory Improvement Amendments (CLIA) and undergo regulatory review by the College of American Pathologists (CAP), state agencies such as the New York State Department of Health (NYS-DOH), and other agencies. Mayo Clinic believes that additional layers of regulatory structure, including FDA approval, are not the answer to perceived problems with LDTs. We believe that the appropriate response is to update CLIA and add necessary requirements such as clinical validity, adverse event reporting, quality systems, post-market surveillance, etc. The 21st century modernization of the regulatory framework for LDTs

needs to occur through updates to CLIA regulations rather than through additional FDA regulation of LDTs.

The primary principles that we strive for when performing laboratory testing for our patients at Mayo Clinic and our Mayo Medical Laboratories patients at other hospitals in the United States and throughout the world include: 1) The needs of the patient are always at the center of our practice with a deep commitment to patient safety, 2) We use modern technologies and systems to provide the highest quality laboratory results for our patients, 3) We only offer clinically validated and useful testing to our physician colleagues and patient care givers, and 4) We ensure that all patients have access to the highest quality laboratory testing. All of our LDTs at Mayo Clinic and Mayo Medical Laboratories meet these principles.

LDTs are fundamentally different than in vitro diagnostics (IVDs). LDTs are not kits and there is no manufacturing of supplies. LDTs are test protocols and services that clinical laboratories develop and validate in their laboratories and then offer to physicians as they evaluate and care for their patients. LDTs are not sold as kits to other laboratories or facilities, but are ordered by physicians as a request for a service. Literally thousands of laboratory tests in this country are LDTs and these range from routine tests to complex molecular genetic tests with complicated analyses. LDTs cover the spectrum of medical care from inpatients to outpatients, are used by all medical specialties, and can provide diagnostic, screening, prognostic, and/or therapeutic information. These tests provide physicians with important clinical information and thus are crucial to the practice of medicine. Although LDTs that assess for inherited and somatic gene mutations in hereditary disorders and cancer has been the primary public focus of the FDA, other types of LDTs (e.g., non-molecular/genetic tests, such as mass spectrometry and a variety of assays for all types of infectious agents) would also be greatly affected by these guidelines.

LDTs are often at the forefront of medical innovation and are used to quickly bring novel scientific and medical discoveries to the bedside.

**Clinical example of an LDT rapidly made available to patients:**

Mutations of the calreticulin (CALR) gene were discovered to play an important diagnostic and prognostic role in myeloproliferative neoplasms, such as primary myelofibrosis and essential thrombocythemia. This discovery was first announced at the American Society of Hematology national meeting in December 2013. By March 2014, Mayo Clinic and Mayo Medical Laboratories were able to offer a high quality, safe, and clinically validated CALR assay to both Mayo Clinic physicians as well physicians across the entire United States.

This is an example of how an LDT can take an important medical advance and rapidly make it available to patients in a safe and validated way. An FDA-driven review process could never achieve this in any routine way.

The FDA has cited concerns about the quality and safety of LDTs as the primary impetus for developing its guidelines and believes that laboratory-testing errors are common and have caused patient harm, especially as testing becomes more technologically complex. The FDA asserts that this additional oversight will assure safety and quality. While an admirable goal, there is no data to support the FDA's contention and its proposed guidelines may result in greater harm than benefit to patients. Indeed data from Mayo Clinic would suggest that such concerns are not warranted and that significant patient safety issues do not exist if the clinical laboratory follows the four principles outlined above. Mayo Clinic rigorously reports and collects all sentinel events related to patient safety and adverse and unexpected outcomes. These are submitted by patients, employees, or providers and are evaluated by an institutional sentinel event office to understand the root cause

and to improve processes to prevent events from happening again. We use this same process for our Mayo Medical Laboratories clients and our clients report events they encounter back to us.

**Data from a clinical laboratory practice:**

Over the course of the last 6 years, we have performed over 2.5 million LDTs for Mayo Clinic patients. We have had zero sentinel events over that time period related to the design or validation of those LDTs. Going back even further, we cannot ever recall a sentinel event for Mayo patients related to the design of an LDT. Furthermore, we have performed over 19 million of these same LDTs for our MML clients and have had zero sentinel events reported to us that relate to the design or validation of those LDTs. In total, over 21 million LDT tests were performed in this time frame and zero sentinel events were reported relative to the design of those LDTs. These outcomes are not unique to Mayo Clinic. As we proceed with this regulatory reform, we need to be sure that we understand what the real problem or issues are before we institute arbitrary changes that create unforeseen problems and issues.

Clinical diagnostic laboratories have been highly regulated for decades by the Clinical Laboratory Improvement Amendments (CLIA). This law requires that laboratory testing be performed in a licensed laboratory, by qualified personnel, and with robust quality systems and controls in place. CLIA also requires full analytical validation of LDTs (i.e., determinations of accuracy, reproducibility, analytical sensitivity, analytical specificity, and other test-performance characteristics) in order to assure reliable and safe test results.

The regulatory requirements for a clinical laboratory are not insignificant. Currently, Mayo Clinic holds 141 separate CLIA certificates, in addition to 31 separate state permits to perform laboratory testing, including permits for New York. Mayo Clinic laboratories are accredited by either the College of American Pathologists (CAP) or The Joint Commission (TJC) and also hold specialty accreditations by AABB, the American Society of Histocompatibility and Immunogenetics (ASHI), and others. For non-waived CLIA certificates, inspections by deemed accreditation agencies occur biennial with an additional inspection by NYS-DOH Clinical Lab Evaluation Program (CLEP). As a new test is added to the laboratory test listing, updates to the test listing are made to CLIA and deemed accreditation agencies in addition to test submission protocols that are submitted to New York State (CLEP) program for review/approval. As part of the accreditation inspection process, new tests are reviewed including proficiency testing and alternative assessment outcomes.

**Practice of Medicine, Conduct of a Test, Development and Manufacturing**

*Question #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?*

The clinical laboratory is more complex than what usually appears to those outside of the laboratory. It is a compliment to the dedication of laboratory professionals that have allowed these complex activities to function every day in a smooth and coordinated way. The three constituents outlined in the question above are separate and it is important that clear and logical lines be drawn when understanding the end-to-end laboratory process. Those constituents include: 1) kits, reagents, and instruments that are manufactured and sold for use in a clinical laboratory by IVD manufacturers. These are regulated by the FDA; 2) the operational activities within a clinical laboratory that produces the laboratory results for a requesting physician. These are regulated by CLIA; and 3) laboratory test protocols and services (i.e., an LDT) that are developed by a laboratory physician for use as requested by a clinical physician. This aspect involves the practice of medicine and is the interface between the operational laboratory and the patient receiving care via laboratory testing. Although there may be aspects of this latter constituent that have regulatory

expectations (such as quality systems, clinical validity, etc.), the majority of this activity uses skills that rely on the practice of medicine. We would like to highlight each of these and focus on the differences between the development of an LDT (which represents the practice of medicine) and manufactured kits from IVD manufacturers.

Commercially available diagnostic kits are actual packages that can be labeled and shipped to clinical laboratories. They are not sold to the clinician seeing the patient, the clinician never sees that kit, and everything that happens after the manufacturers have sold the reagent/test kit is out of the manufacturer's sphere of influence and responsibility. Clinical laboratories in various settings (academic center, rural hospital, inpatient, outpatient, etc.) use these kits. Under CLIA regulations, the laboratory is required to verify that the performance characteristics of the FDA approved/cleared test system are reproducible in the CLIA laboratory (verification of performance). The laboratory physician has to be assured that those kits meet the appropriate and desired analytical and clinical validation for their setting. The laboratory physician then has to make a medical determination on how those kits should be used – to which part of the medical practice should they be offered, how reports will be generated, what additional information needs to be provided to the clinicians with the request, etc. Once that kit reaches the clinical laboratory, the IVD manufacturer turns over the responsibility of performing and reporting to the clinical laboratory physician.

In contrast, LDTs are services that are developed by laboratory physicians for specific patient needs – no different than how an anesthesiologist decides on the best anesthesia to use for a particular patient undergoing surgery. A laboratory medicine physician develops a protocol for a testing service that uses reagents (that are FDA regulated) and laboratory instruments (that are usually FDA regulated). The laboratory physician uses his/her laboratory skills and also his/her own clinical judgment in determining how to develop that LDT protocol to answer a particular clinical question or need. CLIA requires the laboratory to establish performance characteristics for LDTs and requires additional analytical validation requirements for LDTs. CLIA regards LDTs high complexity laboratory testing and dictates the appropriate CLIA certificate and personnel qualifications required to perform these testing services. The laboratory physician uses his/her clinical knowledge to assure that the test can indeed answer the clinical question being asked, to define how the test will be used clinically, define the clinical specimens to be used, and produce a report that will be sent to the medical record and used by the requesting physician. These steps are all part of the LDT development or protocol. The service that is ultimately provided cannot be packaged up into a kit, labeled with instructions and sold on the marketplace. The LDT is not a manufactured product.

***Clinical example of how an FDA-approved kit can have a negative impact on clinical care and restrict access to new and important discoveries:***

BRAF gene mutation detection in malignant melanoma is a textbook example of how regulatory processes cannot keep up with scientific advances and will deter innovative discoveries. The FDA-approved BRAF assay for malignant melanoma only detects V600E mutations. There are additional mutations such as the V600K mutation that the FDA-approved assay does not detect, but that do predict treatment response to Zelboraf (vemurafenib). If required to only use the FDA approved assay, then those additional clinically beneficial mutations would not be detected.

The FDA-approved KRAS assay that is used to make anti-EGFR treatment decisions in patients with colorectal cancer (CRC) only detects mutations in codons 12 and 13 of the KRAS gene. Patients with mutations in KRAS have been shown not to respond to expensive anti-EGFR therapies and in fact sometimes have a detrimental response when given anti-EGFR therapies. It is known that mutations in codons 61 and 146 of the KRAS gene also

predict whether anti-EGFR therapies will have benefit, but the FDA approved tests do not detect these mutations. The National Comprehensive Cancer Network (NCCN) guidelines recommend that these mutations be assessed in CRC patients that are being considered for anti-EGFR therapies. Thus, forcing a laboratory and clinical practice to use just the FDA-approved assay would lead to poor patient care in that some patients with CRC would receive anti-EGFR therapy even though they would not benefit from therapy and sometimes might even do worse than if they had not been treated at all. It should also be noted that the NCCN guidelines also recommend testing CRC patients for NRAS mutations because they also predict to resistance to anti-EGFR therapies. But there is no FDA-approved test for NRAS mutations.

Restricting patient access to only FDA-approved assays will have a negative impact on patient care and will prevent patients from having immediate access to innovative discoveries and applications.

An IVD diagnostic kit does not offer flexibility in how the test is to be used. The end user has to comply with the intended use that is designated with that kit. Results that are generated are typically limited to variables that are specified by the manufacturer. In contrast, LDTs allow the laboratory physician to have a complete understanding of the procedure and its components, its performance limitations, its intended use and intended clinical setting, and the acceptable clinical and analytical validation. A IVD diagnostic kit is manufactured so it can be performed anywhere for a typical patient, whereas an LDT can be designed and validated to meet a specific clinical need and its characteristics can be specifically communicated in consultation (via various tools) with the patient's treating physician.

**Clinical example of how an FDA-approved kit does not guarantee appropriate clinical validation:**

The current FDA review process for laboratory testing does not guarantee that a laboratory test is actually meeting the desired clinical need. For example, the FDA-approved companion diagnostic test kit for ALK gene mutations in lung cancer was validated on resected lung tumors, which are comprised of big pieces of tumor tissue. This is not how medicine is actually practiced where transbronchial needle biopsies and fine needle aspirations account for the majority of specimens being evaluated for lung cancer and their associated therapeutically significant mutations. Thus, the clinical validation for this test that was approved by FDA was not complete and certainly did not reflect how patients are being evaluated in today's clinical practice. Many laboratories are now offering ALK testing on needle biopsies and cytology specimens, via modified FDA validated procedures, to reflect that clinical reality. Submitting a modification back to FDA usually does not happen in this situation as manufacturers find it to be time, cost and paperwork prohibitive – especially for a companion diagnostic kit. By linking the test to the drug, the proposed FDA process will severely inhibit if not totally prevent the ability of clinical laboratories to respond to clinical needs. If restricted to a FDA-approved kit, only a limited number of patients with lung cancer could be tested and thus offered hope, especially if modifications of kits require resubmissions to FDA.

Indeed, the recently endorsed guidelines from the American Society for Clinical Oncology (ASCO) for molecular testing of lung cancer patients cannot be accomplished without LDTs. An FDA approved kit does not guarantee that the right kind of clinical validation has been done.

IVD diagnostic kits are analogous to premade dinners that can be purchased in the grocery store. You're guaranteed a dinner that will have all the desired ingredients. You have no idea how

everything went together and you have no control over how it will taste or how to prepare it. The cook (the laboratory physician) has no choice other than to heat it up and serve it to your family (i.e., the treating physician). If they ask what is in it or if you could make it less spicy, you have no idea. In contrast, LDTs are like the cook (i.e., the laboratory physician) going to the store and purchasing all the necessary ingredients (all of which have passed inspection by government regulations) and bringing them home. A recipe for that meal (the LDT protocol) has been developed by that cook and previously proven to be appetizing and approved by the family. The cook has control over how the meal will taste and knows exactly the quality of the ingredients being used. The cook then follows that recipe, prepares the meal, and delivers it to the family.

The distinction between kits developed by an IVD company versus an LDT developed by a clinical laboratory also differs in how they are distributed. Commercial diagnostic test reagents/kits are products that can be packaged, labeled and shipped in interstate commerce to numerous laboratories. In contrast, the LDT is not a product that can be packaged and shipped to other laboratories. An LDT is a testing service performed in a single CLIA laboratory and is ordered by a physician for a specific patient. Once the manufacturer distributes the commercial reagent/test kit, the manufacturer no longer has control of how the test is conducted, how patients are tested, or what oversight exists for ongoing performance and quality control. Since LDTs are performed in the single CLIA laboratory, the CLIA Lab Director/Technical Supervisor and Clinical Consultant retain ongoing control, knowledge and decision-making about the performance of the LDTs, including patients tested, quality control, proficiency testing and monitoring of performance characteristics. IVD manufacturers are not continually engaged in the performance, interpretation, and quality of an IVD after it has been sold to a lab and IVD manufacturers are not able to continually correlate test results with patient findings.

CLIA laboratories offer testing services to their own local medical facility/health system, but often offer testing services to local community hospitals and clinics that are not a part of their medical facility. In addition, large reference laboratories also offer testing services to patients nationally. For these testing services, the practice of medicine continues with decisions determining clinical information necessary for interpretation of the test and in many cases, conversation with the local ordering provider in specific situations as determined by the laboratory physician as part of the practice of medicine.

Reference laboratories such as Quest, LabCorp, Mayo Medical Laboratories, and ARUP offer their testing services to physicians and their patients across the country and the world. Reference laboratories are staffed by laboratory physicians and other specialists with specialized training in the performance and interpretation of clinical lab tests and that their involvement in test performance, interpretation, and quality continues well after the test is produced and “sold” by the clinical laboratory (i.e. there is an ongoing of “practice of medicine” involved with the tests that clinical laboratories produce). Therefore, additional regulation by the FDA is completely unnecessary and duplicative of existing CLIA oversight.

CLIA has very specific personnel requirements for Laboratory Director, Clinical Consultant, Technical Supervisor, and Testing Personnel. A Clinical Consultant is a M.D. or Ph.D. with board certification in one or more medical specialties of Laboratory Medicine and Pathology and have completed post-graduate medical 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 and for which continued certification is maintained. For example, in the area of laboratory genetics there are specialized board examinations in Clinical Molecular Genetics, Molecular Genetic Pathology, Cytogenetics and Biochemical Genetics.

The operations of a clinical laboratory and the performance of a laboratory test including design, clinical validation, and quality systems should be regulated under CLIA. Based on the complexity of the test, CLIA has specific requirements for testing including personnel qualifications, quality control, proficiency testing and requirements to verify performance characteristics or to establish performance characteristics, which is also the case for LDTs. Conducting a laboratory test is strictly a CLIA laboratory function. CLIA is dedicated to the clinical laboratory and has a long history of understanding the critical issues associated with clinical laboratory testing. Oversight of this key aspect of providing health care needs to stay with those who understand the issues and are the experts. Moving portions of this oversight to another agency charged with overseeing every food, drug, cosmetic, and device that hits the shelf will not improve laboratory performance and will indeed create overlapping confusion.

**For an LDT, what constitutes a “device”**

*Question #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?*

In vitro diagnostics (IVDs) are defined in regulation as a specific subset of medical devices that include “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions ... in order to cure, mitigate, treat, or prevent disease ... [s]uch products are intended for use in the collection, preparation, and examination of specimens taken from the human body.” ( 21 C.F.R. §809.3(a); Definitions.)

Since an LDT is performed within the same CLIA laboratory that developed the LDT, there are no specific products that are moved through interstate commerce appropriate for regulation. In fact, an LDT is a **testing service** based on a protocol developed by the laboratory. As a testing service, it includes the design, development, performance, reporting and interpretation of that service. This clearly constitutes the practice of medicine.

Since there is no easy, clear answer to what constitutes the “device” as it relates to an LDT, it should not be governed as a “device” by FDA. The right course would be to reform CLIA regulations and to add the modules such as design, clinical validation and quality systems that are critical to LDTs. These could include requirements for third party accreditation such as exists through the College of American Pathologists (CAP) - Adverse Event Reporting and Requirements for Clinical Validation. This is far preferable to adding another regulatory process and giving the FDA broad new authorities over LDTs.

One exception to this process would be in the area of Direct to Consumer Testing (DTC). Since the relationships between the ordering physician, the CLIA laboratory conducting the LDT, and the laboratory physician are critical for patient treatment and management, DTC testing needs to be regulated differently. DTC testing should be regulated by the FDA to ensure safety and effectiveness for the consumer (public), since there is no medical professional involved in the interpretation of the test and subsequent patient management.

**Medical Device Classification System Appropriate for LDTs and IVDs**

*Question #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?*

Mayo Clinic generally agrees with other major stakeholders that risks posed by clinical tests are different from therapeutic medical devices. A new risk classification should be developed for clinical laboratory testing. There needs to be significant stakeholder input on this topic as there has never been a consensus from laboratory and clinical professionals as to what constitutes “high” or “medium” risk categories for laboratory tests. There needs to be sufficient flexibility in this definition to balance the relative risks of the test with the potential benefits to the patient. CLIA and third party vendors such as CAP already have the framework to do this and could be given authority to accomplish this task.

Mayo Clinic supports the concept of risk-based regulation of laboratory tests. Risk categorization should be determined by: (1) the potential of a misinterpreted result to cause significant harm, injury or death to a patient, (2) test characteristics, e.g., a test methodology that is not transparent or well-understood (as in the case of tests that use complex algorithms to produce results or those that use proprietary algorithms or computations such that the result cannot be tied to methods used) or for which no standard proficiency testing exists or inter-laboratory comparisons can be performed, and [3] the performance established over time by the performing laboratory for clinical validation, quality systems, adverse event collection and reporting, etc. for LDTs. Consideration of whether the test method is well characterized, well-established and recognized by the medical community, use of published peer reviewed literature, established practice guidelines, etc. should also be criteria considered in establishing the risk categorization.

In the Draft Guidance “ Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) ”, the FDA has stated that high-risk tests will be subject to pre-market approval requirements within 12 months of the guidance being finalized, and that the FDA will release additional guidance on risk classification criteria once its proposed framework is finalized. But it has failed to clearly define the criteria it will use to determine risk. Laboratories are uncertain of how to determine whether the tests they offer are high-risk and subject to pre-market review within 12 months, and unable to effectively plan for the additional effort and manpower that would be required for pre-market submission. We believe it is essential that the FDA clearly define risk classification criteria before subjecting laboratories to burdensome requirements. Further, we find it puzzling that the FDA has already named certain test classes that will be considered high-risk without stating how risk classification criteria were applied to these tests to place them in the high-risk category.

**Pre-Market Review standards for Safety and Effectiveness:**

*Question #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?*

Standards for safety and effectiveness for laboratory tests need to directly align with the analytical and clinical validation of a test, which includes precision, accuracy, reproducibility, analytic and clinical sensitivity and analytic and clinical specificity. The medical device concepts are not the same and do not take the relationships between laboratory physician and ordering physician into account. They do not allow for flexibility for the needs of the patient, or consider the way in which medicine is practiced or changes.

The primary principles that we strive for when performing laboratory testing are centered around safety and effectiveness: 1) The needs of the patient are always at the center of our practice with a deep commitment to patient safety, 2) We use modern technologies and systems to provide the highest quality laboratory results for our patients, 3) We only offer clinically validated and useful

testing to our physician colleagues and patient care givers, and 4) We ensure that all patients have access to the highest quality laboratory testing.

We believe it is appropriate to consider improvements to CLIA and we would encourage the Subcommittee to invite additional discussion on the details of any reforms, which may include clinical validation and adverse event reporting for LDTs and to consider reform of the existing medical device regulations for IVD manufacturers.

**Clinical example of how an FDA-approved kit does not guarantee use of modern laboratory methods and providing the safest possible employee environment:**

The current FDA approval process has not helped clinical laboratories that try to protect the health of their employees. The FDA-approved test kit for BRAF testing requires the use of xylene to deparaffinize embedded lung tissue. Modern clinical laboratories have eliminated the use of xylene wherever possible in trying to provide the safest environment for their employees. It was extremely disheartening for laboratory employees to see the FDA-approved kit endorse such methods in for this assay. This is an example of how an FDA-approved kit does not always guarantee that it uses the best and most modern of laboratory methods.

**Pre-Market Review versus Post-Market Controls:**

*Question #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?*

The terms of pre-market review and post market surveillance are not well understood by the CLIA laboratory since these would be new requirements as defined by FFDCa. We are very concerned pre-market review has a long established history of being “slow” and costly. It is our understanding that FDA approved very few new applications in 2014. This rate of approval needs to be understood within the context of the demand that would exist if pre-market review were required for all new LDTs or modifications of existing LDTs. For example, Mayo Clinic annually launches over 150 new LDTs and there are thousands of LDTs used in this country. If premarket approval or post-market controls become necessary to assess the thousands of LDTs that are used to meet today’s healthcare needs, these will impede innovation and result in less access for patients to important laboratory testing. The fees associated with this process, together with the significant increase in local administrative costs to assemble and meet those increased requirements, will add tremendous incremental costs to the healthcare environment at a time when it can least absorb those costs – especially costs that are not used to improve the value of care we provide our patients.

From a CLIA laboratory perspective, CLIA requires proficiency testing (PT), either purchased PT or alternative assessment to ensure ongoing precision, accuracy and quality of testing. If a laboratory fails two PT assessments in a row, that laboratory must provide a documented response plan to ensure the quality of the test. In addition, ongoing clinical correlation studies can be conducted to continue to monitor the ongoing effectiveness of the LDT. CLIA requires laboratories to perform PT twice a year for each analyte tested as a core component of the CLIA program. PT testing is reviewed and signed by the CLIA Laboratory Director and/or designee. These activities are already occurring for tests performed in the CLIA laboratory and should be considered as post-market processes. On-site inspections by deemed authorities such as CAP are also a part of this current post-market review process.

New York State Department of Health (NYS-DOH) Clinical Laboratory Evaluation Program (CLEP) requires a review process for LDTs offered to patients in NYS, which could be considered a pre-market process that could be established for a clinical laboratory. NYS-DOH has developed a

number of test categories with specific submission requirements necessary for LDT approval. NYS-DOH allows the LDT to be performed on patients prior to final approval, as long as all the appropriate information has been submitted and the submitting laboratory has an acceptable track record of performing analytical and clinical validation, proficiency testing, quality systems, etc. Review and study of the NYS-DOH model may provide key insight on an alternative review process that would provide the oversight that FDA desires. NYS-DOH also inspects laboratories biennially to confirm their acceptance for testing NYS patients. Since Mayo Medical Laboratories is a national reference laboratory, our LDTs have received NYS-DOH review and approval.

We understand that IVD manufacturers have concerns about the balance of pre-market and post-market review processes. Due to the limited number of approvals annually for IVDs, we would conclude the processes are slow and costly with existing processes and philosophy. Consideration of new approaches for pre-market review for both diagnostic laboratories and IVD manufacturers need to be considered as part of this regulatory reform.

### **Modifications and Supplemental Pre-Market Review:**

*Question 6: Modifications and supplemental pre-market review*

*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?*

Mayo Clinic disagrees with the concept of pre-market review as we understand it in the medical device industry. However, should a pre-market approval process become necessary, we would argue only significant changes to the intended use of a previously approved submission should require supplemental pre-market approval. Changes should be assessed by the risk classification of the LDT with only high-risk changes requiring an approval. High-risk changes may include changes in the intended use of the test; changes to patient population; specimen matrix, or test type (prognostic, diagnostic, therapeutic), or qualitative versus quantitative changes. Required approvals beyond such changes will only serve to impede a laboratory's ability to keep pace with the practice of medicine.

Currently, CLIA recognizes these same levels of changes to FDA approved/cleared tests as significant and requires the same level of analytical validation in the CLIA Laboratory as would be required for a LDTs.

### **Medical Product "labeling" for diagnostic tests.**

*Question #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 CLIA laboratory is ultimately the consumer of the IVD test kits, as it turns these test kits into testing services that are provided to the physicians and the medical practice. The labels on the IVD products/kits are used by the laboratory and the laboratory physician to determine what is appropriate for the test interpretation and whether additional reporting comments are needed for use by the ordering physician. Much of the information included in the IVD label is utilized directly by the laboratory, as the laboratory sets criteria for verification of testing performance of the IVD –

accuracy, precision reportable range, reference range, specimen requirements, specimen storage and stability, limitations of use, controls, quality control parameters, lot numbers, etc. There is no labeling appropriate for the ordering physician.

When ordering a test for a patient, the ordering physician should have a clear understanding of what a test measures, what methodology is used, what is the appropriate specimen type, what are the limitations of using the test, whether the test is predictive, and what clinical information should be submitted with the order. Much of this information can be readily provided in a listing of laboratory testing services or a laboratory test catalog.

The FDA does not require manufacturers to provide labelling for ordering physicians. It should not create another layer of labeling that only applies to LDTs, when such requirements do not exist for device manufacturers today.

Inclusion of labeling information on patient test reports should be at the discretion of the laboratory physician. This is the practice of medicine and requires medical judgment. Test reports need to clearly and accurately convey test results information. Reports should not be cluttered with information not needed for patient management and medical treatment as that unnecessary material may lead to the physician not finding the critical information needed to care for that patient. CLIA, in fact, prohibits the cluttering of reports with unnecessary information.

Labelling in the traditional sense as labelling a package or container does not apply to an LDT, since the LDT is a testing service offered to physicians and providers and is not a product that is manufactured, packaged and distributed to other laboratories.

### **Overlap between CLIA and FDA Quality Systems**

*Question #8: The Section 1143 guidance documents raise important questions about the relationship between the FFDCA 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?*

We agree that the Subcommittee is asking the right questions, but the FDA's draft guidance does not provide sufficient detail to ascertain where CLIA requirements end and where the FDA requirements might begin. The FDA has promised a cross-walk between the CLIA Quality System requirements and FDA Quality System Regulations (QSRs); however we are still waiting for this information. Whether LDT or IVD, the FDA does not dispute that performance, interpretation, and reporting of laboratory testing is solely under CLIA oversight. We strongly urge this Subcommittee to consider the compelling need to avoid duplicative and confusing regulation and oversight by two federal agencies, but also by a number of states and separate accreditation bodies with deeming authority. Any duplicative regulation will lead to confusion in the laboratories, will not improve medical practice, and will only add to the costs of an already expensive healthcare system and will do so without any improvement in the quality of laboratory testing services provided.

CLIA quality system requirements are focused on the performance of laboratory testing whereas the FDA QSRs are focused on design controls and manufacture of the reagents/kits (products). Not only do we anticipate areas of overlap that will only add confusion to laboratory testing, we also believe these two quality systems are designed for different purposes and will not solve the issues the FDA has expressed.

The FDA has proposed a framework for regulation of LDTs, but has not clarified or produced any documentation of coordination with CMS, which is charged with administering CLIA compliance. Just as Congress charged the FDA, the Federal Communications Commission, and the U.S. Department of Health & Human Services Office of the National Coordinator for Health Information Technology to jointly develop a proposed regulatory framework for digital health to avoid duplicative and burdensome regulation, there is an urgent need to require CMS and the FDA to engage major stakeholders in a transparent process and propose a framework that clearly and specifically identifies areas where the agencies will avoid contradictory, overlapping and or/and ambiguous oversight parameters.

Reportedly, 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 Subcommittee 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 the proposal before it is finalized through notice and comment processes. We are concerned that the FDA has already demonstrated that it lacks the bandwidth to expand oversight to laboratory developed testing services when it is unable to produce a guidance document promised years prior and which multiple stakeholders have requested in order to provide meaningful and informed comment on the FDA's proposed new and far reaching regulation.

### **Tests for Rare Diseases, Unmet Needs, Emergency Use**

*Question #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)?*

Overall, the majority of clinical tests performed for rare diseases and unmet needs are LDTs and have been regulated under the current CLIA regulations. These tests have not typically been manufactured by IVD companies due to low volumes of tests overall, which does not make them desirable candidates for IVD manufacturers. Current costs of bringing a test through the FDA processes are prohibitive when tests are of low volume. Any regulatory system that addresses diagnostic tests used for rare diseases, unmet needs and emergency use must be flexible in order to provide patient access to these very important testing services and any associated fees need to be considered in context of overall volumes.

The proposed application of the FDA regulatory framework to testing services for rare diseases, unmet needs, or emergency use — even with exemptions and carves out will limit the availability of these very important testing services to individual patients and for public health purposes. In the FDA guidance document, Framework for Oversight of Laboratory Developed Tests”, it states that: *“If an IVD is being developed to help diagnose a disease or condition with an incidence of fewer than 4000 patients per year, but there are more than 4000 patients subject to testing using the device, than the device does not qualify as HUD.”*

From a practical standpoint, if only 4000 patients are subjected to testing then the actual number of patients with that disease will be exceedingly small. In diseases that are rare, testing for those disorders is often performed to “rule-out” that disease. It is not uncommon to see a positivity rate of 10% or less due to the fact that only rare patients would actually have a “positive” test result. The proposed definition would be so limited as to have virtually no test that would meet that requirement. The numeric definition of rare disease needs to be looked at scientifically to

determine the appropriate threshold, would likely be significantly higher than 4000, and preferably tied to the incidence of disease rather than the volume of tests performed.

**Clinical example of how the rare disease exception is insufficient to meet public health demands:**

The expansion of testing in newborns for serious and life-threatening disorders has been a significant improvement in public health. Most of these disorders are exceedingly rare but have significant life-long impact on those babies, their families and the public health as a whole. Since the volumes of these tests would far exceed the proposed FDA definition of a rare disease, each of the dozens of newborn screening tests would have to go through the FDA-approval process. The burden of this process would force both private as well as public laboratories to either reduce the number of screening tests offered or to simply not offer it at all.

It was also stated in the guidance document that: “Laboratories are encouraged to seek approval under Humanitarian Device Exemption (HDE)”. Based on that statement it is unclear how FDA plans to proceed with this carve out. Applying for Humanitarian Exception for the many rare diseases would require a great investment of time and might in many instances deter developing tests for such diseases. Consequently this requirement would lead to a complete lack of availability of such testing for patients.

For Mayo Clinic, we will not have any tests that fall into two of the carve-outs (traditional LDTs and Unmet Needs) because, according to the FDA’s definition, LDTs can only be offered to patients within a single medical facility unless it has FDA-approval for that test. This definition is very limiting to all reference laboratories and would seriously limit the ability for Mayo Clinic to offer our experience and our services to our current Mayo Medical Laboratories’ clients. Currently we offer our large menu of LDTs, including those that have been developed due to unmet needs, to clients through Mayo Medical Laboratories. Virtually all academic center laboratories and large hospitals within a metropolitan area will also offer and perform LDT services for their local community physicians, hospitals and clinics. This service is critical for patient care in that community and provides continuity of care and enhanced service because of this local connection.

**Clinical examples of how restrictions of LDTs will have a negative impact on their availability to patients:**

LDTs are often superior to the comparable FDA-approved kits. The mass spectrometry LDT assay for vitamin D testing significantly outperforms the FDA approved immunoassay for Vitamin D. The immunoassay is cross-reactive with other analytes and also fails to detect the D2 subtype. FDA-approved serologic tests for chronic hepatitis E virus in organ transplants are unreliable and only LDT molecular tests are available. If restricted to FDA-approved kits, we could not offer the highest quality testing and care to all patients we serve – we could not offer hope to our patients.

FDA has commented that LDTs were appropriate back in 1976 when they were restricted to local practices since consultation was available between the pathologist and ordering physician, and LDTs should continue to be restricted in the same way in 2015. The reality is that today’s communication and information availability was unimaginable in 1976. Rotary phones, hand-typed memos, and paper medical records versus today’s electronic medical records, email, cell phones, web portals, computers, and electronic catalogs, with all being available 24 hours a day, 7 days a week. Today, consultation between pathologist and physician can easily occur anywhere in ways that couldn’t be comprehended yesterday. We can provide monitoring of our services and meaningful consultation with physicians even when “our patients” are at a distance. This is today’s practice of medicine. Having an FDA approved test won’t cut out the need for this communication

and may even create a false sense of security that discourages these communications. The medical facility definition should not apply since the laboratory physician and laboratory scientist can access critical patient information via direct communication with the ordering physician.

The nature of public health outbreaks demands that health systems respond rapidly. Due to our test development and innovation over the past decades, Mayo Clinic was able to respond to the anthrax scare, H1N1 outbreak, and have identified new microorganisms because of our investment in new technologies, methodologies, and LDTs. A rapid clinical response was made possible because we were already invested in these new methods and technologies. We understood them and how they should be used, which then made application in an emergent situation effective. In the future, if the academic medical centers and reference laboratories are not able to invest in these new methods and technologies because of costs to take LDTs through the FDA process, we will be limited in how we can respond to critical medical needs. The reliance will then shift to the IVD manufacturers, who may not have the right incentives to proceed in meeting those needs. In order to respond quickly in an emergent environment, one relies heavily on laboratory investments with new methods and new technologies that have occurred over many years.

### **Transition**

*Question # 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?*

Mayo Clinic does not support a new regulatory system. Rather, it believes strongly that modernizing CLIA oversight of laboratories is the best way to address the issues with minimal impact. Any congressional action to modify the existing oversight and regulation should grandfather in the vast majority of existing LDTs until a specific historical problem is articulated and demonstrated. In addition, Congress must consider that Medicare’s reduction in coverage and reimbursement in the context of testing services will coincide with the significantly increased costs of additional and burdensome oversight and regulatory obligations. We strongly urge the Subcommittee to consider the interplay between these dynamics and the impact they will have on patient access to existing laboratory testing services as well as the impact it will have on future innovation of laboratory healthcare.

### **Incentives:**

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

Overall, clinical laboratories and in vitro diagnostic manufacturers all want the same thing: high quality testing services that are analytically and clinically validated; the application of modern technologies to meet the needs of rapidly evolving medical practices; access for all patients who need these innovative and critical testing services; and reduction of the overall cost structure within the healthcare system that does not compromise quality or safety. As we consider these goals, the regulatory framework that is put into place needs to focus on these principles – whether it involves modernization of CLIA, significantly changing the medical device regulations for IVD manufacturers, and /or reforming payment systems for critical testing services based on overall value to the health system. Regulatory fees that are applied to diagnostic tests will need to be balanced with the overall costs of these tests within the healthcare system and regulatory test fees cannot outweigh or inhibit the healthcare benefit that would arise from their use.

**Conclusion and recommendations:**

Increasing duplicative regulatory oversight has the potential to create three conflicting agendas: 1) A shrinking number of facilities providing LDTs due to the constraints and limitations of regulatory processes; 2) Limiting access to LDTs to only a few and selective laboratories; and 3) Increasing demand by patients for access to high quality and innovative care as provided for by LDTs. When these three contradictory agendas are forced together, the consequence will result in restricting innovation when it is needed most. The unfortunate outcome of such a convergence will have the potential to negatively impact and ultimately harm our patient care efforts.

Mayo Clinic believes that additional layers of regulatory structure and FDA approval are not the answer to perceived problems with LDTs. We believe the focus should be on updating CLIA. If there is a need to ensure clinical validity, then add clinical validity requirements to CLIA. If there is a need to understand problems through “post market surveillance”, then find a mechanism under CLIA to measure patient events arising from testing systems. We need to be sure that we understand how laboratory tests are actually used in the practice of medicine before agencies blindly apply device regulations to what they believe might be the practice of medicine. Before we add additional regulatory processes, we need to be certain that we understand the scope of the problem that actually exists, that the proposed solution will actually improve and not impede patient care, that the proposed solution will not restrict access to laboratory testing necessary for patient care, and we need to ensure that there is a realistic cost to benefit ratio for any new regulatory program.

Mayo Clinic recommends changes to the regulatory framework must include:

- Modernization and enhancement of CLIA with appropriate requirements for LDTs. These requirements may include clinical validation, adverse event reporting, appropriate labeling requirements and strengthening the role of third party review and accreditation. Modernization will maintain the ability of laboratories to provide rapid responses to changes from evolving medical technologies and scientific knowledge.
- Regulatory guidelines that do not limit the abilities of physicians to practice medicine. The development of LDTs and their role in patient care is the practice of medicine for pathologists and laboratory physicians. The pathologist, laboratory physician, and laboratory scientist all have an important role in the interpretation of sophisticated laboratory assay results and can help assure that complex laboratory testing is used and interpreted appropriately.
- Recognition that reference laboratories can provide safe, accurate, and clinically validated LDTs for hospitals, clinics and physicians who are outside their health care facilities. Requiring FDA-approval for all LDTs performed in a reference laboratory setting will severely limit innovative health care and will restrict access of quality laboratory care to the patients who need it most.
- Acknowledgment that rapid changes are occurring in health care organizations and that traditional hospital-based laboratories can provide appropriate laboratory services, including safe, accurate, and clinically validated LDTs, for their entire network, as well as providing laboratory support for the communities in which they reside.
- Mayo Clinic supports the concept of risk-based regulation of laboratory tests. However, the definition of any high-risk test category must be done cautiously and with well-defined, consensus-driven criteria. The unintended consequences of loosely defined categories will lead to confusion in clinical laboratories and inhibit development of new and novel assays.
- Any additional regulatory oversight must take into account the incremental costs that will be added to the overall healthcare system. These costs may be related to fees, significantly increased administrative costs to the healthcare system, and the clinical impact of not having tests available locally for the care of their patient population.

**Feedback to  
*21<sup>st</sup> Century Cures Act***

**A Modernized Framework for Innovative Diagnostic Tests**

From **Creatv MicroTech, Inc.**

Contact: **Pete Amstutz, CFO and VP of Business Development**

240-441-3411, [pete@creatvmicrotech.com](mailto:pete@creatvmicrotech.com)

[www.creatvmicrotech.com](http://www.creatvmicrotech.com)

We are a small cancer diagnostic company with a novel platform technology and a newly identified biomarker. We have developed a platform technology to collect circulating tumor cells (CTCs) from the blood of cancer patients efficiently and rapidly, and we developed a method to identify CTCs accurately. In the process of analyzing patient samples, we found a previously unreported biomarker, another type of cancer associate cells, in the blood of cancer patients and they are giants 4-30 times the size of WBCs.

Our technology and the two biomarkers, CTCs and giant cancer associated cells, are applicable for early detection of cancer, as well as determining therapy, monitoring treatment, and watching for recurrence. It is applicable to all solid tumors, which affect ten million Americans. We are confident that our technology can save lives.

Although the federal government has programs to help small companies conduct medical research, developing a new diagnostic product requires much greater high-risk capital investment. It is difficult for small diagnostic companies to raise this kind of capital for two main reasons: (i) FDA is considering heavier regulatory burden on all diagnostics, and (ii) recent changes in the patent system seriously limit patent protection for diagnostic biomarkers. If you were an investor, would you take that risk now?

The cost of FDA approval for diagnostics can be very high. For a new biomarker diagnostic, separate approval is required for each cancer and for each intended use. The cost of this piecemeal FDA approval for even one cancer is very high and a great challenge for a small company.

The cost alone of FDA approvals for several cancers and multiple intended uses is hard to achieve, which significantly limits the benefits to the patients that need them.

Because new, novel and more accurate tests can no longer be protected by filling patents, due to the change of the patent law, there should be incentive to encourage development of those tests to help the patients.



[www.creatvmicrotech.com](http://www.creatvmicrotech.com)

Most of the time, innovations are from individual inventors or entrepreneurs who have licensed technologies from universities and start small businesses.

Some possible incentives to support innovation and entrepreneurs are:

- Allow CLIA testing of those tests without FDA approval or in the process of obtaining FDA approval.
- Provide interim, provisional FDA approval.
- Allow the results of CLIA tests to be used as data to support FDA approval.
- New program at FDA for diagnostics for small business, like that for Orphan drugs.

In summary, requiring all diagnostics to be FDA approved would slow down the development of diagnostics and severely limit the availability of innovative diagnostics for the patients.



1227 25th St. NW #700  
Washington, DC 20037  
combinationproducts.com  
202.861.1881



September 8, 2014

**VIA ELECTRONIC DELIVERY**

The Honorable Joe Pitts, Chairman  
Subcommittee on Health  
Committee on Energy and Commerce  
2125 Rayburn House Office Building.  
Washington, D.C. 20515

The Honorable Frank Pallone, Jr.  
Ranking Member  
Subcommittee on Health  
Committee on Energy and Commerce  
237 Cannon House Office Building  
Washington, D.C. 20515

Re: September 9, 2014 LDT Hearing;  
Statement for the Record

Dear Congressmen Pitts and Pallone:

The Combination Products Coalition (“CPC”) offers the following statement into the record for the Subcommittee on Health’s September 9, 2014 hearing entitled “21st Century Cures: Examining the Regulation of Laboratory Developed Tests.”

The CPC believes that FDA’s decision to submit its framework for LDT regulation to Congress is a significant step forward in continuing the conversation regarding the best regulation for diagnostic tests. A single, optimized regulatory framework will spur the kind of innovation that is crucial to advancing personalized medicine by ensuring that all test developers – whether working at a clinical laboratory or at a traditional manufacturer – can bring much-needed companion diagnostic tests to patients quickly and safely. The better the tests we have, the better the chances we have of getting patients the right drug at the right dose, which makes finalizing the framework crucial to advancing the public health.

Although FDA would regulate certain LDTs under its proposed framework, CMS would still have a significant role to play. CMS would still regulate laboratory services, continue to inspect labs, and impose its own requirements under the Clinical Laboratory Improvement Amendments of 1988 (“CLIA”). There are legitimate concerns about the potential confusion the overlay of two sets of regulatory requirements from two separate agencies could cause. Thus, to form a single risk-based system for diagnostics that avoids duplication and averts confusion, it is imperative that FDA, CMS, and other stakeholders work together closely on developing a final framework.

Through the 21<sup>st</sup> Century Cures Initiative, Congress could facilitate the regulatory policy process through legislation that requires relevant federal agencies (e.g., FDA and CMS), and other stakeholders, to work together to develop a final regulatory framework within a reasonable timetable. More specifically, Congress could enact legislation similar to that used in FDASIA Section 618, which brought together relevant agencies to develop the framework for health information technology regulation, and authorized a federal advisory committee/working group to offer input into that federal strategy. We encourage you and your colleagues to consider a similar approach in this case.

In addition, as the conversation about LDT regulation proceeds, the other side of the diagnostics equation – tests produced by traditional manufacturers – must be taken into account. Whatever the final system is, it must offer equal flexibility to both laboratories and traditional diagnostic test manufacturers. Elements of FDA's proposed framework for LDTs, such as the use of literature to establish clinical validity of diagnostics – as opposed to costly and time consuming trials manufacturers are often required to perform – would be equally valuable for traditional manufacturers to use to secure FDA clearance for new diagnostics. Here, too, the 21<sup>st</sup> Century Cures Initiative could help by mandating that agencies consider not just LDT regulation, but the entirety of diagnostics regulation, to create a single, and optimal, regulatory system that treats all parties and products equally.

We believe that increasing regulatory flexibility (to accelerate innovations that help patients), and decreasing regulatory burdens on lower-risk diagnostics (to allow greater dedication of limited FDA and industry resources to higher-risk tests), should be hallmarks of the final regulatory system. Further, flexibility and regulatory burdens should be based on what the diagnostic is as opposed to *who* the manufacturer is; whether a diagnostic is made by a traditional manufacturer or a clinical lab, it must meet the same standards of safety and effectiveness, and follow the same regulatory path to patients.

We stand ready to assist you in developing this approach. Please let us know if there is anything we can do to be helpful.

Sincerely,

A large black rectangular redaction box covering the signature area.

Bradley Merrill Thompson  
On Behalf of the Combination Products Coalition



January 5, 2015

**VIA Electronic Mail to: [cures@mail.house.gov](mailto:cures@mail.house.gov)**

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

**RE: 21<sup>st</sup> Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests**

Dear Chairman Upton:

On behalf of the Coalition for 21st Century Medicine (the “Coalition”), I am pleased to respond to your request for responses to the questions you posed to stakeholders regarding the regulation of innovative diagnostic tests.

The Coalition for 21<sup>st</sup> Century Medicine comprises some of the world's most innovative diagnostic technology companies, clinical laboratories, venture capital companies, and patient groups working to support appropriate regulatory oversight and fair reimbursement policies to promote innovation in the development and use of advanced personalized diagnostic testing. Coalition members develop and perform clinical diagnostic testing, so-called laboratory developed tests (“LDTs”), invest in such companies, and also represent patient groups whose members obtain such tests. Given the Coalition’s mission, we have a keen interest in the extent to which the U.S. Food and Drug Administration (“FDA”) intends to regulate LDTs as medical devices<sup>1</sup> as well as in the regulation of *in vitro* diagnostics more broadly.

Below, please find our response to the questions you raised in the above-captioned announcement. (For ease of reference, the Committee’s language is provided in bold text.)

---

<sup>1</sup> The Coalition acknowledges that some groups have questioned whether FDA has the authority under the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 301 et seq.) to regulate LDTs as medical devices, including those that it sought to define for discussion in draft FDA guidance as *In Vitro Multivariate Index Assays* (“IVDMIAs”). The Coalition does not address this question in this response. Consistent with the approach that the Coalition has taken throughout the FDA’s consideration of this issue, the Coalition's comments supportive of certain approaches to regulation should not be considered an acknowledgement by the Coalition or any of its members that FDA has the authority to regulate laboratory services as medical devices. In addition, these comments do not represent an admission by the Coalition or any of its members that any particular laboratory service is a “device” as that term is defined under Section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 321(h)).

- 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?**

We agree there should be clear lines separating the development and manufacturing of a diagnostic test, the actual conduct of a diagnostic test, and the practice of medicine.

- The “development” of a diagnostic test refers to the steps taken by a manufacturer (in the case of an IVD test kit) or laboratory (in the case of an LDT) with respect to the conception and design of the test.
  - The “manufacturing” of a diagnostic test refers to the process through which the physical materials required to perform a diagnostic test (e.g., reagents, supplies, equipment) are produced.
  - The “actual conduct of a diagnostic test” refers to the procedures that a laboratory follows to collect, prepare and examine specimens taken from the human body, and analyze and report the result(s) of such tests.
  - The “practice of medicine” refers to a medical professional’s interpretation and use of the information provided by a diagnostic test in the diagnosis of disease or other conditions, determination of prognosis, prediction of treatment outcome, and/or treatment selection. The practice of medicine may also include the actual conduct of a diagnostic test by a certified and licensed clinical laboratory as directed by a medical professional.
- 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?**

With respect to both distributed test kits and LDTs, the “device” should be the collection of physical materials required to run the test (e.g., reagents, supplies, equipment—but not the patient sample itself) together with the directions for use. The “development” and “manufacturing” of these materials may be appropriate for regulation by the FDA.

The “actual conduct of a diagnostic test” and “practice of medicine” are already subject to regulation under CLIA, state laboratory licensure, and healing arts laws and should not fall under regulation by the FDA.

- 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?**

In assessing the risk associated with an *in vitro* diagnostic product, the FDA should consider the seriousness of the disease to which a result relates and the materiality of the result to a medical professional's diagnostic, prognostic or therapeutic decision. Diagnostics intended for use in patients with serious conditions and/or that direct a physician to make a particular diagnosis or offer a particular treatment should be considered higher risk than diagnostics intended for use in patients with less serious conditions and/or that provide information that is not by itself determinative with respect to patient management. Of particular importance are the risks associated with any management change indicated by the diagnostic test results and the impact when the results are inaccurate—i.e., the impact of a false negative or a false positive result on patient outcomes.

The risks posed by an *in vitro* diagnostic test differ from those posed by a therapeutic device. While a therapeutic medical device has a direct impact on the structure or function of the body, an *in vitro* diagnostic test's impact is indirect – i.e., it only affects the structure or function of the body insofar as a medical professional uses the result of the test in patient management (unless the test requires an invasive procedure to obtain the specimen that would not otherwise be performed).

The risks associated with LDTs are similar to the risks associated with distributed tests.

Although the traditional medical device classification system is risk-based, it is not appropriate for diagnostic products because of the different risks posed by diagnostic tests (see above). A classification framework for *in vitro* diagnostic tests should focus specifically on the characteristics that are most relevant to the performance and use of an *in vitro* diagnostic test (e.g., analytical and clinical validity).

- 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 concepts of “safety” and “effectiveness” do not speak to the critical elements of diagnostic test performance. Rather, in assessing whether an *in vitro* diagnostic test (whether a test kit or and LDT) functions as claimed, the FDA should consider whether the test is analytically valid (i.e., accurate, reliable, and reproducible) and clinically valid (i.e., that the result reported by the test accurately diagnoses diseases, determines prognosis, or predicts clinical outcomes).

- 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?**

Yes, because of the inherent difficulties of evaluating use of laboratory tests in a clinical setting, we believe in many instances shifting reliance toward post-market processes could improve patient access without significantly compromising health or safety.

Outcomes trials regarding the use of an *in vitro* diagnostic test are difficult to run because they require researchers to link (a) the result of a test to a patient management decision, and (b) the patient management decision to a health outcome. It can be prohibitively expensive to run such

tests – particularly where the outcome of interest is not immediately apparent (e.g., cancer recurrence) – because it may take several years for subjects to reach an endpoint of interest. Researchers may need to enroll large numbers of subjects to ensure the trial has adequate statistical power to account for intervening factors between the diagnostic test and the outcome of interest. Moreover, variability in therapeutic interventions may confound the effect of the diagnostic test on patient outcomes.

Therefore, the FDA should reconsider the balance between the amount and type of clinical data that reasonably can be obtained on a pre-market basis versus through post-market controls. We believe greater emphasis on post-market studies could be particularly important for diagnostic tests that represent substantial improvements over existing diagnostic tests and/or meet significant unmet needs. Further, we encourage the FDA to increase its reliance on published, peer-reviewed articles that are not reports of randomized, controlled trials (e.g., reports from quasi- or non-experimental designs, clinical practice guidelines, nationally or internationally-accepted standards) when assessing a diagnostic test.

FDA should also consider the technical and economic feasibility of pre-market as well as post-market trials and the studies that the Agency requires or recommends that a sponsor conduct. As above, with diagnostic tests for certain diseases or conditions (e.g., early stage breast cancer, prediabetes or prehypertension), studies assessing long-term endpoints would require many years to complete and large numbers of subjects to control for confounding factors. It would not be feasible economically for most diagnostic test sponsors to conduct studies assessing long-term endpoints in these conditions. Even if a sponsor were able to raise the resources to conduct such a study, it is likely that the analytical methodology or bioinformatics would advance substantially over the course of the study such that the results would no longer be relevant once the study is completed.

**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?**

A supplemental application should only be required if a change has a clinically meaningful impact on a test's performance (i.e., the change would reasonably be expected to lead to a change in patient diagnosis, patient prognosis, or prediction of outcome to treatment compared with the expected result using the original test).

Testing methodologies are constantly evolving—especially in molecular testing (e.g., those made possible by dramatic advances in sequencing) as new findings about the relationship of specific gene markers and clinical conditions are reported every day. However, a change in test methodology or the addition of a new marker to a diagnostic test panel will not necessarily change a test's performance. For example, one may have analytically validated a test for reporting specific variants of a particular gene. Insofar as new information is widely available in the published literature about the biological role of specific variants, reference to this information in laboratory test reports should not require pre-market review and clearance/approval by the FDA.

In general, the requirement for submission of a supplemental clearance or approval should not differ between LDTs and distributed test kits.

- 7. We have heard a lot of 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?**

Consistent with other regulated products, the “labeling” for a diagnostic test may include the packaging and any other written, printed, or graphic material that is included with the packaging for or that otherwise accompanies the physical materials that are used in performing the diagnostic test. However, standards for dissemination of scientific information regarding diagnostic tests should differ from the standards applicable to “traditional” medical devices.

The performance of a laboratory test is a medical service. In recognition of this fact, CLIA regulations require laboratories to provide clinical consultation to clients, assist clients in ensuring that appropriate tests are ordered to meet clinical expectations, ensure that reports of test results include patient information required for patient specific interpretation, and ensure that consultation is available and communicated to patients on matters related to the quality of the test results reported and their interpretation concerning specific patient conditions. Labeling requirements for diagnostic tests should not stand in the way of fulfilling these requirements. Regardless whether information is furnished by a laboratory or a manufacturer of a distributed kit, information that is truthful and non-misleading should be lawful to disseminate. The standards for dissemination of scientific information for diagnostic tests should recognize that for many tests the manufacturer and the provider of the test are the same entity.

- 8. The Section 1143 guidance documents raise important questions about the relationship between the FFDCIA 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 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?**

There is considerable overlap between the requirements outlined in the draft LDT guidance documents and those promulgated under CLIA. For example, FDA and CLIA have similar – but not identical – quality systems requirements with respect to management responsibility, quality audits, personnel requirements, document controls, purchasing controls, identification and traceability, production and process controls, inspection, measuring and test equipment, general recordkeeping, servicing, and statistical techniques. (We have attached a summary table that compares the FDA and CLIA quality systems requirements--see Appendix.)

Establishing a single, consolidated set of requirements would enhance provider understanding of the requirements that may apply to their activities.

**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., rare cancers or blood disorders, Ebola)?**

An expedited regulatory pathway should be made available to manufacturers and laboratories that develop diagnostic tests used for rare diseases and diagnostic tests needed for emergency or unmet needs.

In defining what constitutes a “rare” disease, the FDA should consider its criteria for designating orphan conditions (e.g., that the disease or condition affects fewer than 200,000 people in the United States [total prevalent population]). Although the FDA has a device-specific exemption for rare conditions (the humanitarian device exemption (HDE)), this exemption is available only for devices intended to treat or diagnose a disease that affects fewer than 4,000 people in the United States per year. Because *in vitro* diagnostics are often used for purposes of treatment selection – i.e., to identify a subset of patients with a condition in whom a treatment may be appropriate – it would be appropriate to make “rare” status available to conditions consistent with those used to designate orphan drugs.

Customized diagnostic tests – i.e., tests developed by an individual provider for use with an individual patient – should not be subject to regulation by the FDA. (The development and performance of such tests should be considered as part of the practice of medicine.)

**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?**

Insofar as a novel regulatory scheme is developed for diagnostic tests,

- Existing distributed test kits – i.e., tests that are currently regulated as medical devices by the FDA – should be allowed, for a period of time after the implementation of the new framework, to comply with the requirements for medical devices under the FFDCAs or the requirements of a new diagnostics-specific framework. After a period of time, a previous approval or clearance under the FFDCAs should be deemed an approval under the new framework, and distributed test kits should be required to comply with the regulatory requirements established under the new scheme.
- Existing LDTs should continue to be under enforcement discretion for a period of time after the implementation of the new framework. Eventually, however, an LDT should be required to obtain an approval from the FDA to the extent such approval is required under the new framework. In deciding which LDTs should be subject to the regulatory scheme first, the FDA should prioritize the LDTs that pose the greatest risk to patient health based on a risk scheme that has been proposed, vetted by the public, and adopted through regulation prior to implementation so that providers have sufficient notice and time to adapt to the new regulatory process.
- New distributed test kits should, for a period of time after the implementation of the new framework, be permitted to submit a marketing application as either a medical device

under FFDCa or under the new framework applicable to diagnostics. Insofar as a new distributed kit is approved or cleared under the FFDCa, such approval or clearance should be deemed an approval under the new framework at the same time such deeming occurs for existing distributed tests.

- New LDTs should be required to comply with the new regulatory framework from the date of implementation of the statute. This may involve notification and adverse event reporting when requirements for such notification and adverse event reporting under the new framework are implemented. With respect to pre-market submission, this should follow the same prioritization as for existing LDTs, above, considering which LDTs pose the greatest risk to patient health.

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

The development of new, more accurate, or more efficient diagnostic tests may be encouraged by (a) the provision of a priority review voucher to the sponsor of an innovative diagnostic test and/or (b) the establishment of a Medicare reimbursement premium for laboratories that perform an innovative diagnostic test.

\* \* \* \*

We hope that you have found these comments helpful. If you have any questions about our comments, please contact Mitch Nelles, Ph.D., at 415.287.2374 or via e-mail [mnelles@CareDxInc.com](mailto:mnelles@CareDxInc.com).

Sincerely yours,

/s/

Coalition for 21<sup>st</sup> Century Medicine

**Appendix – Comparison of FDA and CLIA Quality Systems Requirements**

<b>Requirement</b>	<b>Applies to Manufacturers (of test kits)?</b>	<b>Applies to Laboratories (performing LDTs)?</b>
<b>Quality systems requirements</b>		
<b>Management responsibility (for implementing quality system)</b>	√	√
<b>Quality audits</b>	√	√
<b>Personnel requirements</b>	√	√
<b>Design controls</b>		
<b>Design controls</b>	√	Not required
<b>Document controls</b>		
<b>Document controls*</b>	√	√
<b>Purchasing controls</b>		
<b>Purchasing controls</b>	√	√
<b>Identification and traceability</b>		
<b>Identification</b>	√	√
<b>Production and process controls</b>		
<b>Production and process controls (e.g., environmental, buildings)</b>	√	√
<b>Inspection, measuring and test equipment</b>	√	√
<b>Acceptance activities</b>		
<b>Receiving, in-process, and finished device acceptance</b>	√	Not required
<b>Acceptance status</b>	√	Not required
<b>Nonconforming product</b>		
<b>Nonconforming product</b>	√	Not required
<b>Corrective and preventive action</b>		
<b>Corrective and preventive action</b>	√	√
<b>Labeling and packaging control</b>		
<b>Device labeling</b>	√	Not required

<b>Requirement</b>	<b>Applies to Manufacturers (of test kits)?</b>	<b>Applies to Laboratories (performing LDTs)?</b>
<b>Device packaging</b>	√	Not required
<b>Handling, storage, distribution, and installation</b>		
<b>Handling</b>	√	Not required
<b>Storage</b>	√	Not required
<b>Distribution</b>	√	Not required
<b>Installation</b>	√	Not required
<b>Records</b>		
<b>General requirements (recordkeeping)</b>	√	√
<b>Device master record</b>	√	Not required
<b>Device history record</b>	√	Not required
<b>Quality system record</b>	√	Not required
<b>Complaint files</b>	√	√
<b>Servicing</b>		
<b>Servicing</b>	√	√
<b>Statistical techniques</b>		
<b>Statistical techniques (for establishing, controlling and/or verifying acceptability of process capability and product characteristics)</b>	√	√