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Comments of the Association for Molecular Pathology

For the Food and Drug Administration Division of Dockets Management (HFA-305)

Re: Docket # FDA-2011-D-0360

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Comments submitted electronically at www.regulations.gov

The Association for Molecular Pathology (AMP) appreciates the opportunity to submit these comments on the draft guidance titled, "Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)." 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.

I. Introduction

Laboratory developed testing services represent a vital area of medical practice and have historically been central to the advancement of patient care and public health. Clinically valid tests are usually first introduced as laboratory developed services, typically at the request of and in consultation with treating physician colleagues. These testing services are tools in the hands of board-certified specialist physicians, geneticists, and other doctoral level laboratory professionals who apply their professional, scientific, and medical knowledge to optimize patient care. A nimble environment that promotes innovation and allows testing services to be quickly adapted and improved by appropriately qualified professionals is central to the continued advancement of personalized, or precision, medicine.

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

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 boards. They continue to maintain their certification as required and they insure their professional practice activities with medical malpractice insurance.

FDA has proposed to apply the medical device regulations contained in 21 CFR Chapter I Subchapter H to laboratories that provide services utilizing an, as of yet, undefined number of LDPs currently in existence. AMP believes the proposed framework threatens to bring about severe restrictions on physician and patient access to the important health information LDPs provide for patients afflicted with severe infections, cancer, inherited diseases, and other disorders important to the public health.

Laboratory developed testing services are not "plug & play" test systems, but are procedures comprised of a collection of components that may include FDA cleared or approved IVDs, ASRs, general purpose reagents, and instruments. Currently, FDA only regulates individual components of an LDP such as reagents and instruments, 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. While highly trained molecular pathology professionals validate and verify every step and use of reagents and instruments, it is impractical and unnecessary for a lab to refile with FDA for modifications or adjustments to these components.

Current medical device regulations were designed for massively produced boxed and shipped laboratory kits and test systems 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.

FDA must recognize that most, if not all, AMP members lack the legal, administrative, and regulatory expertise, as well as the monetary means, to prepare and submit a single Premarket Approval (PMA) application. Preparation and submission of even a less comprehensive 510(k) application is beyond the financial and administrative capacity of most laboratories. Therefore, if FDA requires premarket submission for a test or category of tests, the Agency should understand that our members will likely be unable to offer it, and therefore, FDA will have in effect significantly diminished or eliminated patient and physician access to the particular service or services.

The implementation of the framework in the draft guidance relies heavily on the intended use of an LDP. FDA will use the intended use of an LDP to classify it based on risk, determine if it meets the definition of an LDP for an unmet need, assess whether it requires earlier premarket review due to the availability of an already cleared or approved LDP with the same intended use, require a subsequent submission for a modification that alters the intended use, and more. For this reason, all aspects of the use of intended use in regulation of

medical devices and diagnostic tests are critical to our ability to understand and consider the implications of such a framework. FDA needs to clarify the definition in great detail providing complete explanations of elements required to comprise a statement of intended use, and about whether and how a patient population, addition of a marker, and how all other variations applicable to an LDP will impact the intended use.

In filing comments on this proposed guidance document, AMP does not waive any legal claim that the FDA lacks the statutory authority to regulate laboratory developed testing services. Furthermore, AMP strongly maintains that, to the extent that it is established that the FDA does have such authority, the overwhelming weight of legal authority dictates that the proposed new requirements for laboratories outlined in the draft guidance must be issued through notice and comment rulemaking. Nothing in these comments is intended to impact adversely in any way AMP's right, alone or in combination with other stakeholders, to pursue separate comments, litigation, or other remedies with respect to the proposed regulatory framework or related issues.

II. Medical Device Regulations are poorly suited for, and inapplicable to, the oversight of laboratory developed procedures.

In its Draft Guidance, FDA has emphasized four categories of regulation:
1) Establishment Registration and Device Listing for Manufacturers in 21 CFR Part 807, for which "Notification" can serve as a surrogate; 2) Medical device reporting, particularly Manufacturer Reporting Requirements in 21 CFR Part 803, Subpart E; 3) Premarket review in 21 CFR Part 807, Subpart and 21 CFR Part 814; and 4) the Quality System Regulation at 21 CFR Part 820. AMP believes that medical device manufacturing regulations are poorly suited for and inapplicable to the oversight of LDPs.

Laboratories are currently among the most heavily regulated health care providers in the United States. Application of manufacturing regulations intended for medical devices or in vitro diagnostic test kits that are manufactured, packaged, labeled, and sold to a wide variety of users throughout the country and over which the vendor has no control, is inappropriate for most LDPs. Not only are such regulations duplicative of preexisting CLIA regulations, but unlike CLIA, they are focused on monitoring and documentation of intermediate activities and steps like design control, rather than the accuracy and reliability of the test results themselves. We believe that FDA in its proposal has artificially separated the provision of LDP services into manufacturing and testing components. In reality, these processes are inextricably linked in a clinical laboratory. Test design, ongoing monitoring, continual test evolution, and the generation, interpretation, and communication of patient specific test results to ordering providers are all tightly interconnected. Because of the fundamental differences in the nature of LDP services and the design and manufacture of test systems that are intended for sale and physical

distribution, patients will be far better served if perceived regulatory gaps and stakeholder concerns are addressed through modernization of the Centers for Medicare and Medicaid Services' CLIA program.

Among the factors FDA regulations instruct the FDA Commissioner to consider for "determining the safety and effectiveness of a device for purposes of classification, establishment of performance standards for class II devices, and premarket approval of class III devices" are: "1) The persons for whose use the device is represented or intended; 2) The conditions of use for the device, including conditions of use prescribed, recommended or suggested in the labeling or advertising of the device and other conditions of use; 3) *The probable benefit to health from use of the device weighed against any probable injury or illness from such use; and 4) The reliability of the device.*" (21 CFR 860.7)

Because one or more of these factors will often differ between LDPs and IVD test kits, we ask any third party reviewer to develop a separate risk paradigm for LDPs that considers the totality of the circumstances surrounding the test offering, including both the reliability and understandability of the method and the level of skill of the professionals involved in offering the test, with adequate weight given to the probable benefits from use of the test relative to the potential harms. AMP believes that a non-traditional regulatory pathway best suits LDPs. FDA has created special 510k pathways (e.g., "Accelerated") to better suit other regulated products, yet has failed to explore this option in their proposed framework for regulating LDPs. FDA should work with stakeholders before finalizing the draft guidance to better address the distinction between LDPs and distributed tests as it applies to a how LDPs should be regulated.

In addition, see comments in Section VIII, Non-Traditional Regulatory Pathways below.

III. AMP requests that FDA provide clarity on how they intend to apply the definition of intended use (21 CFR 801.4) to:

1. **Classify an LDP based on risk;**
2. **Determine if a test meets the definition of an LDP for an unmet need;**
3. **Assess whether it requires earlier premarket review due to the availability of an already cleared or approved LDP with the same intended use; and**
4. **Determine if a test requires a subsequent submission for a modification;**

In addition, FDA should considering using "indications for use" instead.

The proposed regulations rely heavily on the concept of intended use in many aspects of the proposed framework for regulating LDPs. FDA needs to clarify and provide great detail on how the definition of intended use will impact FDA's regulation of LDPs, specifically in the four areas indicated above. In general, AMP recommends broadly defining the unmet needs and traditional LDP categories to account for functional

differences in tests by, for example, applying the narrower concept of "indications for use" rather than "intended use" as currently utilized in substantial equivalence determinations.

Risk Classification

In addition to clarifying the use and definition of intended use, FDA should publish an additional guidance on risk classification before this guidance is finalized. AMP understands that intended use is the primary feature of the test that will be considered. However, FDA should also consider complexity and transparency of the technology and mechanism by which results are derived as well. 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, 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 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 subject to pre-introduction review 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 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, existing and new, 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), which 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 (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 is expected to 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 the tests’ accuracy and reliability. Additionally, those performing high-complexity tests must, under CLIA, undergo regular proficiency testing. Many laboratories obtain CLIA certification through accreditation by CMS-approved accrediting agencies such the College of American Pathologists (CAP) or the Joint Committee on Hospital Accreditation, or obtain CLIA certificates through licensure from CLIA exempt states. The standards of the accreditation program or state in aggregate must meet or exceed those of the CLIA regulations. The programs often go well beyond CLIA including more stringent requirements for proficiency testing, as well as documentation of clinical validity.

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, AMP believes it is inappropriate for 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, 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.

Companion Diagnostics

FDA has declared companion diagnostics to be a priority area of enforcement. In so doing, FDA appears to be considering the risks posed by companion diagnostics solely based on intended use, seemingly irrespective of technology or the professional skill of those who design, develop, oversee the performance of, interpret, report, and communicate the results of LDP testing. AMP disagrees with this approach, and does not believe that tests that are used to guide therapy, even when a test is paired with a specific drug should automatically be placed in Class III. Moreover, we do not believe that IVD test kits and LDPs should necessarily be treated identically in this regard. Accurate test results that are used to guide therapy are essential. However, a laboratory that performs an LDP using reliable and widely performed methods under the direction of skilled professionals, presents a different level of risk than that posed by a proprietary test kit that is manufactured, packaged, labeled, sold and shipped to a wide variety of end users over whom the vendor has no control.

Off-label Use of FDA Cleared or Approved Tests

FDA has proposed designating laboratories that modify cleared or approved tests as remanufacturers, subjecting them to premarket submission requirements under 21 CFR 807.81(a)(3) and 21 CFR Part 814, as well as the Quality System Regulation at 21 CFR Part 820. FDA has stated that intended use "may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised." (21 CFR 801.4) This suggests that oral comments made by a laboratory medical professional would change the intended use and cause FDA to enforce medical device requirements onto the laboratory as the manufacturer. AMP is

concerned that molecular pathologists will be unable to have candid conversations that would benefit the patient and potentially lead to new and important uses of an LDP, even in cases in which the information conveyed by the pathologist is neither false nor misleading. In addition, FDA requires that laboratories that modify a test in a way that affects intended use submit a premarket review application (see the next subsection below). AMP believes that medical professionals in the laboratory, when they validate modifications, are not acting as "re-manufacturers" but as medical professionals using FDA cleared or approved tests off-label. Most laboratories will not have the resources to set up a medical affairs or compliance department with the appropriate personnel to handle these issues, further burdening pathologists with the responsibility of acting as a both a medical practitioner and manufacturer.

Restricting health care professionals from using tests off-label infringes on the practice of medicine. The Food, Drug, and Cosmetic Act addresses the issue of the practice of medicine and states the following:

> *"Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."*[ii]

Off-label use of FDA cleared or approved tests is very common, and can range from employment of different nucleic acid extraction systems, to alternative specimens, sample matrices, or test purposes. The reasons for this variation include highly specific, overly restrictive labeling that is inconsistent with automation or other aspects of laboratory work flow, the ability of laboratories to improve test kit performance, and clear, demonstrable patient needs. For many tests, once DNA of acceptable quality is obtained, its source becomes irrelevant.

Our treating physician colleagues increasingly obtain specimens by less invasive means than in the past. As a consequence, laboratories need to process and test smaller specimens from tissue types prepared and stored in different matrices than those for which a test was originally cleared or approved. Performing testing on a fine needle aspirate, for example, may spare a patient an open biopsy or allow testing in a patient from whom a specimen could not otherwise be obtained. Performing this type of testing serves patient needs, and laboratories that offer such testing employ highly skilled physicians and scientists for whom clinical and analytical validation of off-label uses of tests are well within the scope of their medical practice. Therefore, we strongly urge FDA to re-evaluate the concept of intended use for IVDs and to permit off-label use of IVD kits as it does in other medical contexts involving cleared or approved products.

While we understand FDA's rationale for proposing elimination of enforcement discretion for premarket review for LDPs when an FDA cleared or approved test kit becomes available for purchase, we strongly disagree with this proposed policy. We are deeply concerned that if an LDP is cleared or approved before a packaged IVD

test kit, FDA may no longer consider other LDPs that test for the same analyte as LDPs for unmet needs. This could result in the highly undesirable circumstance in which a single lab is granted a monopoly for a given test.

Test monopolies of this nature are contrary to public interest and adverse to public health because they remove competition in testing services thereby raising costs, reducing patient access, eliminating opportunities for confirmatory (second opinion) testing, decreasing innovation, and removing the possibility of basic quality control measures such as proficiency testing. Therefore, we strongly urge FDA to clarify that removal of enforcement discretion for an LDP in the unmet needs category would be premised on widespread availability of an FDA cleared or approved test kit, rather than clearance or approval of a single LDP. In addition, see the LDPs for Unmet Needs and FDA's Use of Intended Use subsection below.

Modifications

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 as defined above, and should not be based on intended use. 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 expedited.

AMP views modifications to FDA approved or cleared tests as off-label use, and therefore the comments in the previous section apply here.

LDPs for Unmet Needs and FDA's Use of Intended Use

"LDPs for Unmet Needs" likely represents the most important category of testing for patients, ordering physicians, and laboratory providers. AMP shares and appreciates FDA's recognition of the role LDPs play in providing essential services to patients. However, we are concerned that FDA's removal of an LDP from the unmet needs category based on clearance or approval of a test with the same "intended use" could potentially disrupt patient access to tests with distinguishing features that continue to represent important, unmet clinical needs.

For example, the TheraScreen® KRAS RGQ PCR KIT as described on FDA's website, "is intended to aid in the identification of CRC patients for treatment with Erbitux (cetuximab) and Vectibix (panitumumab) based on a KRAS no mutation detected test result."[iii] Adopting this broad description of the utility of the test as its

"intended use" would mandate that all labs that perform *extended* KRAS testing for prediction of cetuximab response, as recommended in the 2015 National Comprehensive Cancer Network Colon Cancer guidelines, submit their tests for premarket approval.

Because PMA submission is beyond the capability of virtually all laboratories, they would discontinue offering *extended* KRAS tests even though TheraScreen® fails to meet this demonstrable medical need. The TheraScreen® KRAS test's indications for use as quoted from FDA's website state that the test is "indicated for: the Therascreen® KRAS RGQ PCR Kit is a real-time qualitative PCR assay used on the RotorGene Q MDx instrument for the detection of seven somatic mutations in the human KRAS oncogene, using DNA extracted from formalin fixed paraffin-embedded (FFPE), colorectal cancer (CRC) tissue."[iv] By adopting this indication for use rather than utilizing the broad description presented in the previous paragraph, FDA would more accurately identify those tests for cetuximab responsiveness in colorectal cancer patients that continue to satisfy an unmet need.

FDA has historically maintained a broad conception of intended use that has biased medical device classification toward Class II, thereby allowing medical device manufacturers to avoid the more onerous premarket approval process in favor of 510(k) clearance. However, applying a broad view of intended use when considering enforcement discretion for LDPs for unmet needs would grossly disadvantage clinical laboratories, their ordering physicians, and their patients. Thus, FDA will need to either adopt a different standard for intended use when determining whether an LDP satisfies the unmet need requirements, such as indications for use as recommended in the previous paragraph, or narrow its conception and application of intended use more generally. Whether an unmet need has been sufficiently met is a complex issue that cannot be easily solved by using the concept of intended use. FDA should use expert advisory panels to evaluate whether any given need has been met across the United States. We suggest the following composition for advisory committees:

- Expert in molecular pathology
- Physician who orders molecular diagnostics
- Physician who conducts and reports test results
- Representative from the diagnostics kit manufacturing industry
- Representative from a sole source/proprietary lab
- Representative from a hospital, academic medical center or clinic-based lab
- Representative from a large, national reference lab
- Representative from a pharmaceutical manufacturer
- Patient who has benefited from molecular diagnostics
- Representative from CMS's CLIA program involved in laboratory regulation

- Representative for the Centers for Disease Control and Prevention experienced with laboratory regulation
- Third-party accreditor with deemed status within the CLIA program.

Finally, FDA should be aware that the single gene, single drug testing paradigm is rapidly becoming outmoded, as multi-analyte testing using next generation sequencing to guide therapy is becoming the standard of care for mutation testing. Because of the revolutionary nature of this exciting new technology, the speed with which it is advancing, and the explosion of knowledge about how best to incorporate this testing, FDA approval of test kits that will meet the continually changing needs of patients and physicians will be enormously challenging. To date there are no such FDA approved tests available for use. Thus, as in the previous discussion, we urge FDA to apply the more narrow specific indications for use of cleared or approved next generation sequencing tests, to determine whether a given LDP next generation sequencing test is considered to meet an unmet need. We note that FDA has released a white paper, concepts which will be the subject of a February 20, 2015 workshop. We look forward to engaging the Agency in discussions of this important technology and these concepts, a number of which seem to indicate a better understanding of the role of medical professionals and clinical laboratory testing utilizing next generation sequencing. However, we also note that there could be considerable conflict between proposed regulation arising from the white paper and this draft framework and urge the Agency to withdraw this draft guidance and pursue notice and comment rulemaking, particularly in light of lack of clarity around the use of Intended Use, LDPs for unmet needs, and utilization of next generation sequencing. Please see sections II, VIII, and IX for additional information.

IV. AMP urges FDA to expand the definition of hospital or health system to include specimens acquired from external patients, and to refrain from enforcing premarket review requirements against hospital and health system laboratories that accept external patient specimens.

FDA proposes to implement premarket review for all moderate and high risk LDPs, but has stated it will not enforce these requirements against "traditional" LDPs, and LDPs for "unmet needs." FDA also intends to designate laboratories that modify a cleared or approved test as remanufacturers, necessitating the filing of premarket submissions by these laboratories, and subjecting them to compliance with the Quality System Regulation at 21 CFR Part 820. These proposed extensions of medical device regulations raise complex questions and importantly, pose significant risks to patient access to essential medical services.

LDPs for Unmet Needs and FDA's Restriction to Patients in the Same Health System as the Laboratory

FDA has rightfully proposed exempting LDPs for unmet needs from premarket review. However, we are

concerned that the Agency has limited this category in a manner that will disadvantage ordering physicians and be detrimental to patients. FDA has proposed restricting the designation as LDPs for unmet needs to those tests offered by hospitals and health systems solely for patients diagnosed and/or treated within the same facility or health care system. FDA should consider that an LDP that is cleared or approved for an intended use but its use is restrictive to a single health system does not meet the need of patients in the community or other health systems.

We acknowledge and agree with FDA's contention that the common responsibility shared by hospitals and health systems and their laboratories creates and encourages the implementation of multiple safeguards that help ensure high quality clinically and analytically valid testing. However, we believe many of these safeguards also apply to specimens from external patients sent to hospital and health system laboratories because the same tests, processes, and procedures are applied to external patient samples as are applied to samples originating within the institution or health system itself.

External patients who utilize hospital and health system laboratories are often registered in the institution's electronic medical record system, and typically have the same access to specialty expertise for consultation regarding their laboratory results as hospital and health system patients. Finally, the internal expertise and reputational considerations attached to such entities ensures that they offer reliable, clinically and analytically valid, and medically useful testing.

Hospitals and medical centers often perform testing for external patients for analytes for which volumes are too low in the local facility to justify offering such tests internally. In addition, such testing may require greater medical and technical expertise than is available locally. Thus, even for hospital and health system reference laboratories the economics of premarket submission and compliance with the Quality System Regulation for such tests would be unfavorable, and would likely cause these important providers to cease offering many critical tests. Therefore, on behalf of our patients and our treating physician colleagues, we urge FDA to extend the definition of hospital and health system to include specimens received from external patients.

Moreover, while these processes and safeguards are present in medical centers, they are not necessarily unique to them. Commercial reference laboratories can install many of the same elements discussed above, and a number currently do. FDA should recognize that independent laboratories existing outside a healthcare system may have additional types of safeguards in place that encourage reliable, clinically and analytically valid testing. These laboratories also provide essential services to patients and physicians.

Traditional LDPs

Much of the testing performed in a modern pathology laboratory falls outside the rubric of how FDA has defined a "traditional" LDP in the draft guidance. However, key traditional test areas include immunohistochemistry and *in situ* hybridization. Both of these types of testing are visual techniques interpreted by pathologists using conventional brightfield or fluorescence microscopes, and often can be performed in a manner in which they utilize only components that are legally marketed for clinical use.

Therefore, FDA should make clear that LDPs utilizing immunohistochemistry and in situ hybridization technology are pathology services that are exempt from FDA regulation under the Agency's framework. We also urge FDA to adopt the same definition of hospital and healthcare system discussed under unmet needs in order to ensure that external hospital and health system patients continue to benefit from these essential services.

Furthermore, technologies considered to be "traditional" should evolve with time as treating physicians become familiar with them. FDA has acknowledged that they believe that it has become necessary to regulate selected LDPs because they have become complex and the underlying technologies are not easily understood by clinicians. At one time, all new technology can be considered "complex"; previously, FDA has viewed electronic data storage in this manner and mandated that manufacturers maintain paper backups, but has since moved on from this position.

V. AMP agrees that laboratories should not be required to complete registration and listing for LDPs.

AMP believes that it would be inappropriate for the agency to require most laboratories that provide services using LDPs to comply with registration and listing requirements intended for medical device manufacturers. We note that notification would avoid user fees and the medical device tax; however, it will generate significant additional administrative costs for the laboratory in a difficult reimbursement environment. In addition, registration and listing should by definition be inapplicable to providers of diagnostic laboratory services. Currently, laboratories are required to submit lists of their tests to CLIA and may voluntarily participate in the Genetic Testing Registry housed at the National Institutes of Health, as well as other databases. Creating a separate notification system duplicates already existing efforts throughout the government. Further, with the implementation of the Protecting Access to Medicare Act, laboratories are going to be required to provide pricing data to CMS on every laboratory test performed. FDA should consider accessing existing HHS agencies' registries and databases of LDPs in lieu of requiring laboratories to complete an entirely new notification process and/or working with its sister agencies to condense them into a single reporting requirement within HHS. Requiring laboratories to report the same test to multiple federal agencies is not the least administratively burdensome manner to collect this information.

VI. AMP requests that FDA restrict application of the Medical Device Reporting requirements to laboratories that have received approval orders for high risk LDPs.

FDA has proposed applying Medical Device Reporting requirements (MDRs) in 21 CFR Part 803, Subpart E to most laboratories that use LDPs. We believe compliance with these requirements is likely to consume significant administrative resources without accompanying benefits to patient care or gains in patient safety. Instead, we propose limiting application of the MDRs to laboratories that have received approval orders for high risk LDPs (Class III).

Under the MDRs, manufacturers must report to FDA within 30 days of receipt, information that reasonably suggests that a marketed device, "(1) May have caused or contributed to a death or serious injury; or (2) Has malfunctioned and this device or a similar device that you market would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur." (21 CFR 803.50(a)) The regulations define a serious injury as an illness or injury that: "1) Is life-threatening, (2) Results in permanent impairment of a body function or permanent damage to a body structure, or (3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure." "Permanent" means "irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage." Finally, to "cause or contribute to" a death or serious injury means "that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of: (1) Failure; (2) Malfunction; (3) Improper or inadequate design; (4) Manufacture; (5) Labeling; or (6) User error." (21 CFR 803.30)

Our members' experience performing thousands of laboratory tests over many years suggests to us that the risk that the vast majority of LDPs would cause or contribute to a death or serious injury as defined by FDA regulations is exceedingly low. In addition, CLIA already requires labs to report errors in test results to ordering physicians. The pertinent CLIA regulation, 42 CFR 493.1291, reads: "Standard: Test report. (k) When errors in the reported patient test results are detected, the laboratory must do the following:
(1) Promptly notify the authorized person ordering the test and, if applicable, the individual using the test results of reporting errors. (2) Issue corrected reports promptly to the authorized person ordering the test and, if applicable, the individual using the test results. (3) Maintain duplicates of the original report, as well as the corrected report."

Despite the low likelihood of contributing positively to patient care, extension of the MDRs to our members' laboratories would necessitate that they develop policies and procedures for reporting adverse events as well as an infrastructure to analyze potential adverse events, including maintenance of records of

investigations and analyses. (21 CFR 803.17, 21 CFR 803.18) Although the costs of establishing and implementing processes and procedures, as well as the documentation ongoing analyses would require are non-trivial, the overwhelmingly likelihood is that the extensive surveillance our members would need to pursue would not yield any reportable events. Therefore, if FDA requires clinical laboratories to comply with the MDRs, we believe enforcement should be limited to those LDPs most likely to present serious risks to patients, namely those for which premarket approval has been required and obtained.

VII. AMP asks FDA to limit application of the Quality System Regulation (21 CFR Part 820) to laboratories that have submitted premarket approval applications for Class III LDPs.

As FDA acknowledges, the CLIA regulations address the ultimate desired outcome of "the ability to perform testing in an accurate and reliable manner." (Draft Guidance p. 7) The intermediate, surrogate focus of the medical device manufacturing regulations is a practical necessity for regulatory oversight of distributed test kits, but is misplaced in the context of LDPs wherein the data regarding quality and reliability of the test result itself are accessible and in fact already extensively regulated. Thus, assigning these proposed requirements, along with already existing CLIA regulations, is unsuitable for most LDPs. Preexisting CLIA regulations ensure a test gives accurate results and, therefore, inherently ensure proper test performance and design. In an area of great concern to AMP members, genotyping has generally proved highly reliable as reflected in many publications in the peer reviewed literature, and most significantly, in published data from the College of American Pathologists' (CAP) proficiency testing program.[v]

The highly detailed CLIA regulations consume 121 pages of the Code of Federal Regulations and track the preanalytic, analytic, and postanalytic phases of testing. The regulations emphasize development of and compliance with written policies and procedures. Laboratories must continually monitor, assess, evaluate, improve, and correct identified problems in their systems and processes throughout all phases of testing and for general laboratory operations, including patient confidentiality, specimen identification and integrity, complaint documentation and investigation, evaluation of proficiency testing (PT) performance, and competency. They must review the effectiveness of their assessments and corrective actions, revise policies and procedures as necessary to prevent recurrences of problems, discuss the assessment activities and findings with appropriate staff, and document all assessment activities.[vi]

The CLIA regulations contain strict standards for quality systems, PT, record keeping, facilities administration, certification, personnel, and inspections, as well as provisions for user fees, enforcement, and sanctions. Clinical aspects of assays are addressed by director and clinical consultant requirements and responsibilities, as well as preanalytic requirements. Proficiency testing or an alternative means of performance

assessment is mandated at least twice per year. (Ibid.)

CLIA also specifies processes for new test validation. For unmodified FDA cleared or approved systems, laboratories must verify the performance specifications established by the manufacturer for accuracy, precision, and reportable range of test results, including verification that the manufacturer's reference intervals are appropriate for the laboratory's population. Laboratories that modify an FDA cleared or approved test system or introduce a test system not subject to FDA clearance or approval must establish as applicable: accuracy, precision, analytical sensitivity, analytical specificity to include interfering substances, the reportable range of test results, reference intervals, and any other performance characteristics required for test performance. (Ibid.)

Many laboratories obtain CLIA certification through accreditation by CMS-approved accrediting agencies such the CAP or the Joint Committee on Hospital Accreditation, or obtain CLIA certificates through licensure from CLIA exempt states. The standards of the accreditation program or state in aggregate must meet or exceed those of the CLIA regulations. The programs often go well beyond CLIA including more stringent requirements for PT, as well as documentation of clinical validity. (Ibid.)

Therefore, we believe application of the quality system regulation to laboratories other than those that have submitted premarket approval applications for Class III LDPs would be excessive and unjustified.

VIII. Other issues

Non-Traditional Regulatory Pathways

In FDA's 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.

Clinical Validity Using Well-Established Technologies and Methods

Although we agree with the use of published literature to support clinical validity, we are concerned with FDA's statement that the sponsor "needs to demonstrate that any changes in technology or methodology that differ from literature to assess the analyte/marker do not affect the clinical validity of the LDT." Many laboratories perform testing using well-validated methods, the effectiveness and accuracy of which have been demonstrated and knowledge of limitations well-established. Therefore, value of such methods should not have to be repeatedly reproved in different tests by different providers and for other analytes. Once, for example, sequencing is established as a platform, there is no further need for review on an individual basis.

Rare Diseases Exemption

FDA has proposed withholding enforcement of Premarket Review Requirements and the Quality System Regulation for LDPs for Rare Diseases, which has defined as tests for which the number of persons who may be tested nationally is fewer than 4000/year. FDA's reasoning is based on the humanitarian device exemption, 21 U.S.C. 360j(m), which states,

> "(1) To the extent consistent with the protection of the public health and safety and with ethical standards, it is the purpose of this subsection to encourage the discovery and use of devices intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States.
>
> (2) The Secretary may grant a request for an exemption from the effectiveness requirements of sections 360d and 360e of this title for a device for which the Secretary finds that—
>
> > (A) the device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States …"

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.

Although the statute specifies that the exemption applies to devices designed to treat or diagnose *a condition that affects fewer than 4,000 individuals in the United States,* FDA has by regulation limited this exemption to 4,000 tests rather than patients, as seemingly required by the statute. Thus, 21 CFR 814.102(a)(5) reads, "If the device is for diagnostic purposes, the documentation must demonstrate that fewer than 4,000 patients per year would be subjected to diagnosis by the device in the United States." FDA's narrow definition of rare disease would limit the significance of this exemption because test numbers for patients suspected of having even very rare diseases are often several-fold higher than the numbers of patients who actually have the disease. For example, many inherited diseases have phenotypic presentations that do not point to a definitive diagnosis. Therefore, differential diagnostic testing is essential.

AMP believes FDA's definition of rare disease is far too restrictive. 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 LDPs 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 tax-payer funds to support applications to the FDA. In addition, because these tests often constitute a small volume of testing for most laboratories, FDA oversight could 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.

Enforcement Discretion for HLA testing

AMP agrees with FDA that performance of HLA testing used in CLIA-certified, high complexity histocompatibility laboratories for transplantation often reflects local considerations based on patient populations and treating physician preferences; that the tests are rapidly evolving; and that enforcement of FDA regulatory requirements "could lead to unavailability of testing." However, we believe these considerations are equally true of most molecular pathology testing and argue against extension of FDA's manufacturing regulations to laboratories that provide molecular pathology services utilizing LDPs. Histocompatibility testing is heavily dependent on LDPs and few FDA approved or cleared tests or components are available. The tests require an elaborate validation process and the laboratories offering this testing are subject to the rigorous accreditation requirements of the American Society for Histocompatibility and Immunogenetics. The parallel to molecular testing for inherited conditions, infectious agents, and cancers is staggering and AMP urges FDA to acknowledge this parallel.

"Devices of Higher Concern to the Agency"

Devices that act like companion diagnostics. FDA has expressed heightened concern about "Those devices that claim to enhance the use of a specific therapeutic product through selection of therapy, patient population, or dose, but which are not included in the therapeutic product labeling." Because of the nature in which FDA labels are generated, and the timing of label changes when they occur, we are concerned that patients could be denied highly beneficial testing due to failure of product labeling to keep up with medical advances with respect to diagnostic test capabilities and knowledge. Moreover, although such tests report results that may be correlated or associated with drug efficacy or side effects, few medical decisions are made in isolation based on a test result alone. Rather, other patient specific factors always govern the medical decision to use specific therapies or treatment modalities, as well as the administered doses.

"Screening devices for serious diseases and/or conditions intended for use in asymptomatic patients" without confirmatory diagnostic products. This category of tests with which FDA has expressed heightened concern is likely to be problematic in practice as FDA attempts to define a workable definition of screening. For example does "screening" only apply to an entirely unselected population or individuals at varying risk levels for a disease? Similarly, the concept of functional confirmation may be equally or more important than specific diagnostic test confirmation. Therefore, FDA will need to establish the meaning and significance of different types of confirmation and apply them on an individual basis to each test to accurately represent risks to individual patients. Ironically, FDA's own proposal may create the very conditions FDA believes represent a

threat to patients by removing the ability of laboratories to provide alternative and competing tests for particular conditions.

Conflicts Among Exemptions and Risk Classifications

The draft guidance fails to address which rules "trump" which rules. For instance, if an LDP is a companion diagnostic and considered high risk by FDA, but is also for a rare disease, is the laboratory still required to complete a PMA or does it meet the exemption for LDPs for rare diseases? The same laboratory procedure can serve a variety of diagnostic purposes. It will be very difficult, if not impossible, for a laboratory to ascertain the ordering physician's purpose in ordering an LDP, and allow certain purposes but prohibit others. This again impinges on the practice of medicine. AMP urges that selection and utilization of laboratory testing be left to medical professionals.

Clinical Investigations

FDA claims that clinical investigations of new laboratory tests do not require informed consent. However, this statement lacks context, and is therefore misleading, as institutional review board (IRB) review is generally demanded of all clinical studies, and IRBs will mandate informed consent whenever such consent is appropriate. Furthermore, this claim contradicts the plain language of 21 CFR 50.

Education

If required to submit 510(k) or PMA applications, this may be only one of many guidance documents and regulations with which medical professionals and laboratories will need to comply. AMP recommends that the FDA provide a catalog or easily accessible library for other documents that will affect laboratories that design and use LDPs on a single webpage on the FDA's website. The FDA should also provide numerous education and training opportunities to laboratories that design and use LDPs.

HIPAA-Compliant Electronic Health Records (EHRs)

FDA should recognize an additional difficulty of applying regulations designed for distributed tests to clinical laboratories. FDA's proposed framework does not take into the consideration that currently mandated/certified EHRs have limitations regarding the information that can be included about a test. Therefore, FDA requirements regarding labeling could be completely incompatible with current EHRs. Also, one of the modifications that a laboratory makes to an FDA approved or cleared test is to ensure that its software outputs are compliant with the new Health Insurance Portability and Accountability Act (HIPAA) Omnibus rule.

If laboratories are prohibited from making these modifications, patient private health information could be at risk of a security breach.

Unique Device Identifiers

AMP recommends continued non-enforcement of the Labeling Requirements of Unique Device Identification in 21 CFR 801 Part B for LDPs, or in the alternative creation of an explicit exemption from these requirements for LDPs. LDPs are not distributed outside laboratories, and therefore are easily identifiable by the laboratories that perform them and the physicians and patients that rely on the test results they produce. Further, the CLIA regulations in 42 CFR 493.43(c)(3) already require laboratories to: "(3) Describe the characteristics of the laboratory operation and the examinations and other test procedures performed by the laboratory including- (i) The name and total number of test procedures and examinations performed annually …; (ii) The methodologies for each laboratory test procedure or examination performed, or both; (iii) The qualifications (educational background, training, and experience) of the personnel directing and supervising the laboratory and performing the examinations and test procedures." This requirement includes LDPs, rendering UDI requirements duplicative and unnecessary. Finally, the infrastructure and IT systems that a laboratory would have to install to comply with this requirement would be cost-prohibitive and overly burdensome without providing a concomitant benefit to patients.

IX. AMP requests that FDA utilize notice and comment rulemaking for the introduction of any final guidance relating to the regulation of laboratory developed procedures.

FDA has proposed an extension of the medical device regulations to a broad category of testing over which it has never exercised jurisdiction and which is already heavily regulated under another federal program. Expansion of FDA regulation to clinical laboratories that provide test services utilizing LDPs would impose substantial new regulatory requirements on the laboratory field, which would likely have profound impacts on patient and physician access to essential laboratory testing, and healthcare generally. Moreover, FDA's proposed framework is heavily dependent on terms such as "laboratory developed test," "LDTs for unmet needs," and "traditional LDT," which have never been defined through regulation. Therefore, AMP believes it is most appropriate for FDA to utilize notice and comment rulemaking before attempting to extend medical device regulations to the laboratory field.

FDA has presented no evidence of a systemic problem with laboratory testing in the United States. Nor has the Agency presented documented evidence that LDPs pose a widespread threat to the public health. Yet the Agency's proposed actions are likely to impose substantial costs and other significant burdens on patients

and providers, including limitations on access to important medical services. In 2011, President Obama issued an Executive Order which provides that:

> *"…each agency must, among other things: i) propose or adopt a regulation only upon a reasoned determination that its benefits justify its costs (recognizing that some benefits and costs are difficult to quantify); ii) tailor its regulations to impose the least burden on society, consistent with obtaining regulatory objectives, taking into account, among other things, and to the extent practicable, the costs of cumulative regulations; iii) select, in choosing among alternative regulatory approaches, those approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity); iv) to the extent feasible, specify performance objectives, rather than specifying the behavior or manner of compliance that regulated entities must adopt; and v) identify and assess available alternatives to direct regulation, including providing economic incentives to encourage the desired behavior, such as user fees or marketable permits, or providing information upon which choices can be made by the public."*[vii]

AMP believes that FDA has not met the President's standard with its draft guidance document. Notice and comment rulemaking would be one means to ensure that FDA complies with the President's directive.

Thank you again for the opportunity to submit these comments on the draft guidance and AMP looks forward to working with federal agencies to design modernized regulations for LDPs that ensure both analytical and clinical validity as well as provide the nimbleness necessary to foster innovation and enable patient access to appropriate testing. If you have any questions or if AMP can be of further assistance, please contact Mary Williams at mwilliams@amp.org or 301-634-7921.

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

[ii] Food, Drug, Cosmetic Act, Subchapter X: Miscellaneous, Section 396. http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapX-sec396.pdf

[iii] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

[iv] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

[v] Weck KE, et al. Molecular genetic testing for fragile X syndrome: laboratory performance on the College of American Pathologists proficiency surveys (2001-2009), Genet Med 2012;14:306-12; Richards CS, et al. Three-year experience of a CAP/ACMG methods-based external proficiency testing program for laboratories offering DNA sequencing for rare inherited disorders. Genet Med 2014;16:25-32; Feldman GL, et al. Results of the College of American Pathology/American College of Medical Genetics and Genomics external proficiency testing from 2006 to 2013 for three conditions prevalent in the Ashkenazi Jewish population. Genet Med. 2014;16:695-702.

[vi] Klein RD. Cancer J;20:85-90.

[vii] Executive Order 13563: Improving Regulation and Regulatory Review. Signed: January 18, 2011. Federal Register: 76 FR 3821, January 21, 2011 p3821 e3823.